

**MAY 2014**  
**STAFF REPORT to the NIDA DIRECTOR**



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## **RESEARCH FINDINGS**

### **BASIC NEUROSCIENCE AND BEHAVIORAL RESEARCH**

#### **Parental THC Exposure Leads to Compulsive Heroin-Seeking and Altered Striatal Synaptic Plasticity in the Subsequent Generation**

Szutorisz H, Dinieri JA, Sweet E, Egervari G, Michaelides M, Carter JM, Ren Y, Miller ML, Blitzer RD, Hurd YL. Neuropsychopharmacology 2014.

Recent attention has been focused on the long-term impact of cannabis exposure, for which experimental animal studies have validated causal relationships between neurobiological and behavioral alterations during the individual's lifetime. Here, the authors show that adolescent exposure to  $\Delta^9$ -tetrahydrocannabinol (THC), the main psychoactive component of cannabis, results in behavioral and neurobiological abnormalities in the subsequent generation of rats as a consequence of parental germline exposure to the drug. Adult F1 offspring that were themselves unexposed to THC displayed increased work effort to self-administer heroin, with enhanced stereotyped behaviors during the period of acute heroin withdrawal. On the molecular level, parental THC exposure was associated with changes in the mRNA expression of cannabinoid, dopamine, and glutamatergic receptor genes in the striatum, a key component of the neuronal circuitry mediating compulsive behaviors and reward sensitivity. Specifically, decreased mRNA and protein levels, as well as NMDA receptor binding were observed in the dorsal striatum of adult offspring as a consequence of germline THC exposure. Electrophysiologically, plasticity was altered at excitatory synapses of the striatal circuitry that is known to mediate compulsive and goal-directed behaviors. These findings demonstrate that parental history of germline THC exposure affects the molecular characteristics of the striatum, can impact offspring phenotype, and could possibly confer enhanced risk for psychiatric disorders in the subsequent generation.

#### **Synaptic Depression Via Mglur1 Positive Allosteric Modulation Suppresses Cue-Induced Cocaine Craving**

Loweth JA, Scheyer AF, Milovanovic M, LaCrosse AL, Flores-Barrera E, Werner CT, Li X, Ford KA, Le T, Olive M F, Szumlinski KK, Tseng KY, Wolf ME. Nat Neurosci. 2014; 17(1): 73-80.

Cue-induced cocaine craving is a major cause of relapse in abstinent addicts. In rats, cue-induced craving progressively intensifies (incubates) during withdrawal from extended-access cocaine self-administration. After ~1 month of withdrawal, incubated craving is mediated by  $\text{Ca}^{2+}$ -permeable AMPA receptors (CP-AMPA) that accumulate in the nucleus accumbens (NAc). The authors found that decreased mGluR1 surface expression in the NAc preceded and enabled CP-AMPA accumulation. Thus, restoring mGluR1 transmission by administering repeated injections of an mGluR1 positive allosteric modulator (PAM) prevented CP-AMPA accumulation and incubation, whereas blocking mGluR1 transmission at even earlier withdrawal times accelerated CP-AMPA accumulation. In studies conducted after prolonged withdrawal, when CP-AMPA levels and cue-induced craving are high, the authors found that systemic administration of an mGluR1 PAM attenuated the expression of incubated craving by reducing CP-AMPA transmission in the NAc to control levels. These results suggest a strategy in which recovering addicts could use a systemically active compound to protect against cue-induced relapse.

#### **C-Ring Cannabinoid Lactones: A Novel Cannabinergic Chemotype**

Sharma R, Nikas SP, Guo JJ, Mallipeddi S, Wood JT, Makriyannis A. ACS Medicinal Chemistry Letters. 2014 Jan 14: A-E. As a part of the authors' controlled-deactivation ligand development project, they recently disclosed a series of (-)- $\Delta^8$ -tetrahydrocannabinols (THCs) with a metabolically labile ester group at the 2'-

position of the side chain. Now, they have replaced the C-ring in the classical THC structure with a hydrolysable seven-membered lactone. One of the synthesized analogues binds with high affinity to the CB1 receptor ( $K_i = 4.6$  nM) and exhibits much lower affinities for the mCB2 and the hCB2. Also, in vitro functional characterization found the compound to be an agonist at rCB1. Consistent with our rational design, the lead cannabinergic lactone identified here is susceptible to metabolic inactivation by plasma esterases, while the respective acid metabolite is inactive at CB receptors. These results are highlighted with molecular modeling of the two regiosomeric lactones.

### **Designer Receptors Show Role For Ventral Pallidum Input To Ventral Tegmental Area In Cocaine Seeking**

Mahler SV, Vazey EM, Beckley JT, Keistler CR, McGlinchey EM, Kaufling J, Wilson SP, Deisseroth K, Woodward JJ, Aston-Jones G. Nat Neurosci. 2014 Apr; 17(4): 577-585. The ventral pallidum is centrally positioned within mesocorticolimbic reward circuits, and its dense projection to the ventral tegmental area (VTA) regulates neuronal activity there. However, the ventral pallidum is a heterogeneous structure, and how this complexity affects its role within wider reward circuits is unclear. The authors found that projections to VTA from the rostral ventral pallidum (RVP), but not the caudal ventral pallidum (CVP), were robustly Fos activated during cue-induced reinstatement of cocaine seeking—a rat model of relapse in addiction. Moreover, designer receptor-mediated transient inactivation of RVP neurons, their terminals in VTA or functional connectivity between RVP and VTA dopamine neurons blocked the ability of drug-associated cues (but not a cocaine prime) to reinstate cocaine seeking. In contrast, CVP neuronal inhibition blocked cocaine-primed, but not cue-induced, reinstatement. This double dissociation in ventral pallidum subregional roles in drug seeking is likely to be important for understanding the mesocorticolimbic circuits underlying reward seeking and addiction.

### **Targeted Expression Of $\mu$ -Opioid Receptors In A Subset Of Striatal Direct-Pathway Neurons Restores Opiate Reward**

Cui Y, Ostlund SB, James AS, Park CS, Ge W, Roberts KW, Mittal N, Murphy NP, Cepeda C, Kieffer BL, Levine MS, Jentsch JD, Walwyn WM, Sun YE, Evans CJ, Maidment NT, Yang X W. Nat Neurosci. 2014; 17(2): 254-261.  $\mu$ -opioid receptors (MORs) are necessary for the analgesic and addictive effects of opioids such as morphine, but the MOR-expressing neuronal populations that mediate the distinct opiate effects remain elusive. Here the authors devised a new conditional bacterial artificial chromosome rescue strategy to show, in mice, that targeted MOR expression in a subpopulation of striatal direct-pathway neurons enriched in the striosome and nucleus accumbens, in an otherwise MOR-null background, restores opiate reward and opiate-induced striatal dopamine release and partially restores motivation to self administer an opiate. However, these mice lack opiate analgesia or withdrawal. The authors used Cre-mediated deletion of the rescued MOR transgene to establish that expression of the MOR transgene in the striatum, rather than in extrastriatal sites, is needed for the restoration of opiate reward. This study demonstrates that a subpopulation of striatal direct-pathway neurons is sufficient to support opiate reward-driven behaviors and provides a new intersectional genetic approach to dissecting neurocircuit-specific gene function in vivo.

### **Cocaine Dysregulates Opioid Gating Of GABA Neurotransmission In the Ventral Pallidum**

Kupchik YM, Scofield MD, Rice KC, Cheng K, Roques BP, Kalivas PW. J Neurosci 2014; 34(3): 1057-1066.

The ventral pallidum (VP) is a target of dense nucleus accumbens projections. Many of these projections coexpress GABA and the neuropeptide enkephalin, a  $\delta$  and  $\mu$  opioid receptor (MOR) ligand. Of these two, the MOR in the VP is known to be involved in reward-related behaviors, such as hedonic responses to palatable food, alcohol intake, and reinstatement of cocaine seeking. Stimulating

MORs in the VP decreases extracellular GABA, indicating that the effects of MORs in the VP on cocaine seeking are via modulating GABA neurotransmission. Here, the authors use whole-cell patch-clamp on a rat model of withdrawal from cocaine self-administration to test the hypothesis that MORs presynaptically regulate GABA transmission in the VP and that cocaine withdrawal changes the interaction between MORs and GABA. They found that in cocaine-extinguished rats pharmacological activation of MORs no longer presynaptically inhibited GABA release, whereas blocking the MORs disinhibited GABA release. Moreover, MOR-dependent long-term depression of GABA neurotransmission in the VP was lost in cocaine-extinguished rats. Last, GABA neurotransmission was found to be tonically suppressed in cocaine-extinguished rats. These substantial synaptic changes indicated that cocaine was increasing tone on MOR receptors. Accordingly, increasing endogenous tone by blocking the enzymatic degradation of enkephalin inhibited GABA neurotransmission in yoked saline rats but not in cocaine-extinguished rats. In conclusion, our results indicate that following withdrawal from cocaine self-administration enkephalin levels in the VP are elevated and the opioid modulation of GABA neurotransmission is impaired. This may contribute to the difficulties withdrawn addicts experience when trying to resist relapse.

#### **Synthesis, Nicotinic Acetylcholine Receptor Binding, and Antinociceptive Properties of 2'-**

**Fluoro-3'-(substituted pyridinyl)-7-deschloroepibatidine Analogues** Ondachi PW, Castro AH, Bartkowiak JM, Luetje CW, Damaj MI, Mascarella SW, Navarro HA, Carroll FI. J Med Chem. 2014 Feb 13; 57(3): 836-848.

2'-Fluoro-3-(substituted pyridine)epibatidine analogues 7a-e and 8a-e were synthesized, and their in vitro and in vivo nAChR properties were determined. 2'-Fluoro-3'-(4"-pyridinyl) deschloroepibatidine (7a) and 2'-fluoro-3'-(3"-pyridinyl)deschloroepibatidine (8a) were synthesized as bioisosteres of the 4'-nitrophenyl lead compounds 5a and 5g. Comparison of the in vitro nAChR properties of 7a and 8a to those of 5a and 5g showed that 7a and 8a had in vitro nAChR properties similar to those of 5a and 5g but both were more selective for the  $\alpha 4\beta 2$ -nAChR relative to the  $\alpha 3\beta 4$ - and  $\alpha 7$ -nAChRs than 5a and 5g. The in vivo nAChR properties in mice of 7a were similar to those of 5a. In contrast, 8a was an agonist in all four mouse acute tests, whereas 5g was active only in a spontaneous activity test. In addition, 5g was a nicotine antagonist in both the tail-flick and hot-plate tests, whereas 8a was an antagonist only in the tail-flick test.

#### **Nicotinic Receptors Regulate The Dynamic Range Of Dopamine Release In Vivo** Koranda JL,

Cone JJ, McGehee DS, Roitman MF, Beeler JA, Zhuang X. J Neurophysiol 2014; 111(1): 103-111. Nicotinic acetylcholine receptors (nAChRs) are expressed presynaptically on dopamine axon terminals, and their activation by endogenous acetylcholine from striatal cholinergic interneurons enhances dopamine release both independently of and in concert with dopamine neuron activity. Acute nAChR inactivation is believed to enhance the contrast between low- and high-frequency dopamine cell activity. Although these studies reveal a key role for acute activation and inactivation of nAChRs in striatal microcircuitry, it remains unknown if chronic inactivation/desensitization of nAChRs can alter dopamine release dynamics. Using in vivo cyclic voltammetry in anaesthetized mice, the authors examined whether chronic inactivation of nAChRs modulates dopamine release across a parametric range of stimulation, varying both frequency and pulse number. Deletion of  $\beta 2^*$ -nAChRs and chronic nicotine exposure greatly diminished dopamine release across the entire range of stimulation parameters. In addition, they observed a facilitation of dopamine release at low frequency and pulse number in wild-type mice that is absent in the  $\beta 2^*$  knockout and chronic nicotine mice. These data suggest that deletion or chronic desensitization of nAChRs reduces the dynamic range of dopamine release in response to dopamine cell activity, decreasing rather than increasing contrast between high and low dopamine activity.

**Impaired Periamygdaloid-Cortex Prodynorphin Is Characteristic Of Opiate Addiction and Depression**

Anderson SAR, Michaelides M, Zarnegar P, Ren Y, Fagergren P, Thanos PK, Wang GJ, Bannon M, Neumaier JF, Keller E, Volkow ND, Hurd YL. J Clin Invest 2013; 123(12): 5334-5341. Negative affect is critical for conferring vulnerability to opiate addiction as reflected by the high comorbidity of opiate abuse with major depressive disorder (MDD). Rodent models implicate amygdala prodynorphin (Pdyn) as a mediator of negative affect; however, evidence of PDYN involvement in human negative affect is limited. Here, the authors found reduced PDYN mRNA expression in the postmortem human amygdala nucleus of the periamygdaloid cortex (PAC) in both heroin abusers and MDD subjects. Similar to humans, rats that chronically self-administered heroin had reduced Pdyn mRNA expression in the PAC at a time point associated with a negative affective state. Using the in vivo functional imaging technology DREAMM (DREADD-assisted metabolic mapping, where DREADD indicates designer receptors exclusively activated by designer drugs), the authors found that selective inhibition of Pdyn-expressing neurons in the rat PAC increased metabolic activity in the extended amygdala, which is a key substrate of the extrahypothalamic brain stress system. In parallel, PAC-specific Pdyn inhibition provoked negative affect-related physiological and behavioral changes. Altogether, this translational study supports a functional role for impaired Pdyn in the PAC in opiate abuse through activation of the stress and negative affect neurocircuitry implicated in addiction vulnerability.

**Dopamine Neurons Control Striatal Cholinergic Neurons via Regionally Heterogeneous Dopamine and Glutamate Signaling**

Chuhma N, Mingote S, Moore H, Rayport S. Neuron 2014; 81(4): 901-912.

Midbrain dopamine neurons fire in bursts conveying salient information. Bursts are associated with pauses in tonic firing of striatal cholinergic interneurons. Although the reciprocal balance of dopamine and acetylcholine in the striatum is well known, how dopamine neurons control cholinergic neurons has not been elucidated. Here, the authors show that dopamine neurons make direct fast dopaminergic and glutamatergic connections with cholinergic interneurons, with regional heterogeneity. Dopamine neurons drive a burst-pause firing sequence in cholinergic interneurons in the medial shell of the nucleus accumbens, mixed actions in the accumbens core, and a pause in the dorsal striatum. This heterogeneity is due mainly to regional variation in dopamine-neuron glutamate cotransmission. A single dose of amphetamine attenuates dopamine neuron connections to cholinergic interneurons with dose-dependent regional specificity. Overall, the present data indicate that dopamine neurons control striatal circuit function via discrete, plastic connections with cholinergic interneurons.

**Mephedrone (4-methylmethcathinone), A Principal Constituent Of Psychoactive Bath Salts, Produces Behavioral Sensitization In Rats**

Gregg RA, Tallarida CS, Reitz A, McCurdy C, Rawls SM. Drug Alcohol Depend 2013; 133(2): 746-750.

The present study tested the hypothesis that mephedrone (MEPH) produces behavioral sensitization (i.e., a progressive increase in motor response during repeated psychostimulant exposure) in rats. MEPH was administered in two paradigms: (1) a 7-day variable-dosing paradigm (15 mg/kg on the first day, 30 mg/kg for 5 days, 15 mg/kg on the last day) and (2) a 5-day constant-dosing paradigm (15 mg/kg for 5 days). Following 10 days of drug absence, rats were challenged with MEPH (15 mg/kg). MEPH challenge produced enhancement of repetitive movement compared to acute MEPH exposure in both paradigms. Sensitization of repetitive movements to MEPH was also detected following a shorter (2-day) absence interval, before initiation of an absence interval (i.e., following repeated daily exposure), and across context-independent and -dependent dosing schedules. A lower dose of MEPH (5mg/kg) did not produce sensitization of repetitive movement. Sensitization of ambulatory activity was not detected in any experimental paradigm. These results suggest that repeated MEPH exposure

produces preferential sensitization to repetitive movement produced by acute MEPH challenge. These findings suggest that MEPH is a unique stimulant displaying weak sensitizing properties with overlapping, but distinctive, features relative to established psychostimulant drugs.

**Functional Status of the Serotonin 5-HT<sub>2C</sub> Receptor (5-HT<sub>2CR</sub>) Drives Interlocked Phenotypes That Precipitate Relapse-Like Behaviors In Cocaine Dependence**

Anastasio NC, Stutz SJ, Fox RG, Sears RM, Emeson RB, DiLeone RJ, O'Neil RT, Fink LH, Li D, Green TA, Moeller FG, Cunningham KA. *Neuropsychopharmacology* 2014; 39(2): 370-382.

Relapse vulnerability in cocaine dependence is rooted in genetic and environmental determinants, and propelled by both impulsivity and the responsivity to cocaine-linked cues ('cue reactivity'). The serotonin (5-hydroxytryptamine, 5-HT) 5-HT<sub>2C</sub> receptor (5-HT<sub>2CR</sub>) within the medial prefrontal cortex (mPFC) is uniquely poised to serve as a strategic nexus to mechanistically control these behaviors. The 5-HT<sub>2CR</sub> functional capacity is regulated by a number of factors including availability of active membrane receptor pools, the composition of the 5-HT<sub>2CR</sub> macromolecular protein complex, and editing of the 5-HT<sub>2CR</sub> pre-mRNA. The one-choice serial reaction time (1-CSRT) task was used to identify impulsive action phenotypes in an outbred rat population before cocaine self-administration and assessment of cue reactivity in the form of lever presses reinforced by the cocaine-associated discrete cue complex during forced abstinence. The 1-CSRT task reliably and reproducibly identified high impulsive (HI) and low impulsive (LI) action phenotypes; HI action predicted high cue reactivity. Lower cortical 5-HT<sub>2CR</sub> membrane protein levels concomitant with higher levels of 5-HT<sub>2CR</sub>:postsynaptic density 95 complex distinguished HI rats from LI rats. The frequency of edited 5-HT<sub>2CR</sub> mRNA variants was elevated with the prediction that the protein population in HI rats favors those isoforms linked to reduced signaling capacity. Genetic loss of the mPFC 5-HT<sub>2CR</sub> induced aggregate impulsive action/cue reactivity, suggesting that depressed cortical 5-HT<sub>2CR</sub> tone confers vulnerability to these interlocked behaviors. Thus, impulsive action and cue reactivity appear to neuromechanistically overlap in rodents, with the 5-HT<sub>2CR</sub> functional status acting as a neural rheostat to regulate, in part, the intersection between these vulnerability behaviors.

**Epigenetic Priming Of Memory Updating During Reconsolidation To Attenuate Remote Fear Memories**

Graff J, Joseph NF, Horn ME, Samiei A, Meng J, Seo J, Rei D, Bero AW, Phan TX, Wagner F, Holson E, Xu J, Sun J, Neve RL, Mach RH, Haggarty SJ, Tsai LH. *Cell*. 2014; 156(1-2): 261-276.

Traumatic events generate some of the most enduring forms of memories. Despite the elevated lifetime prevalence of anxiety disorders, effective strategies to attenuate long-term traumatic memories are scarce. The most efficacious treatments to diminish recent (i.e., day-old) traumata capitalize on memory updating mechanisms during reconsolidation that are initiated upon memory recall. Here, the authors show that, in mice, successful reconsolidation-updating paradigms for recent memories fail to attenuate remote (i.e., month-old) ones. They find that, whereas recent memory recall induces a limited period of hippocampal neuroplasticity mediated, in part, by S-nitrosylation of HDAC2 and histone acetylation, such plasticity is absent for remote memories. However, by using an HDAC2-targeting inhibitor (HDACi) during reconsolidation, even remote memories can be persistently attenuated. This intervention epigenetically primes the expression of neuroplasticity-related genes, which is accompanied by higher metabolic, synaptic, and structural plasticity. Thus, applying HDACis during memory reconsolidation might constitute a treatment option for remote traumata.

### **Ammonia Mediates Methamphetamine-Induced Increases In Glutamate and Excitotoxicity**

Halpin LE, Northrop NA, Yamamoto BK. Neuropsychopharmacology 2014; 39(4): 1031-1038.

Ammonia has been identified to have a significant role in the long-term damage to dopamine and serotonin terminals produced by methamphetamine (METH), but how ammonia contributes to this damage is unknown. Experiments were conducted to identify whether increases in brain ammonia affect METH-induced increases in glutamate and subsequent excitotoxicity. Increases in striatal glutamate were measured using in vivo microdialysis. To examine the role of ammonia in mediating changes in extracellular glutamate after METH exposure, lactulose was used to decrease plasma and brain ammonia. Lactulose is a non-absorbable disaccharide, which alters the intestinal lumen through multiple mechanisms that lead to the increased peripheral excretion of ammonia. METH caused a significant increase in extracellular glutamate that was prevented by lactulose. Lactulose had no effect on METH-induced hyperthermia. To determine if ammonia contributed to excitotoxicity, the effect of METH and lactulose treatment on calpain-mediated spectrin proteolysis was measured. METH significantly increased calpain-specific spectrin breakdown products, and this increase was prevented with lactulose treatment. To examine if ammonia-induced increases in extracellular glutamate were mediated by excitatory amino-acid transporters, the reverse dialysis of ammonia, the glutamate transporter inhibitor, DL-threo- $\beta$ -benzyloxyaspartic acid (TBOA), or the combination of the two directly into the striatum of awake, freely moving rats was conducted. TBOA blocked the increases in extracellular glutamate produced by the reverse dialysis of ammonia. These findings demonstrate that ammonia mediates METH-induced increases in extracellular glutamate through an excitatory amino-acid transporter to cause excitotoxicity.

### **Monoacylglycerol Lipase Inhibition Blocks Chronic Stress-Induced Depressive-Like Behaviors via Activation of mTOR Signaling**

Zhong P, Wang W, Pan B, Liu X, Zhang Z, Long JZ, Zhang HT, Cravatt BF, Liu QS. Neuropsychopharmacology. 2014 Apr; 39(5): 1222-1231.

The endocannabinoid (eCB) system regulates mood, emotion, and stress coping, and dysregulation of the eCB system is critically involved in pathophysiology of depression. The eCB ligand 2-arachidonoylglycerol (2-AG) is inactivated by monoacylglycerol lipase (MAGL). Using chronic unpredictable mild stress (CUS) as a mouse model of depression, the authors examined how 2-AG signaling in the hippocampus was altered in depressive-like states and how this alteration contributed to depressive-like behavior. They report that CUS led to impairment of depolarization-induced suppression of inhibition (DSI) in mouse hippocampal CA1 pyramidal neurons, and this deficiency in 2-AG-mediated retrograde synaptic depression was rescued by MAGL inhibitor JZL184. CUS induced depressive-like behaviors and decreased mammalian target of rapamycin (mTOR) activation in the hippocampus, and these biochemical and behavioral abnormalities were ameliorated by chronic JZL184 treatments. The effects of JZL184 were mediated by cannabinoid CB1 receptors. Genetic deletion of mTOR with adeno-associated viral (AAV) vector carrying the Cre recombinase in the hippocampus of mTORf/f mice recapitulated depressive-like behaviors induced by CUS and abrogated the antidepressant-like effects of chronic JZL184 treatments. These results suggest that CUS decreases eCB-mTOR signaling in the hippocampus, leading to depressive-like behaviors, whereas MAGL inhibitor JZL184 produces antidepressant-like effects through enhancement of eCB-mTOR signaling.

### **Feeding Condition and the Relative Contribution Of Different Dopamine Receptor Subtypes To The Discriminative Stimulus Effects Of Cocaine In Rats**

Baladi MG, Newman AH, France CP. Psychopharmacology (Berl) 2014; 231(3): 581-591.

The contribution of dopamine receptor subtypes in mediating the discriminative stimulus effects of cocaine is not fully established. Many drug discrimination studies use food to maintain responding, necessitating food restriction, which can alter drug effects. This study established stimulus control with



cocaine (10 mg/kg) in free-feeding and food-restricted rats responding under a schedule of stimulus shock termination (SST) and in food-restricted rats responding under a schedule of food presentation to examine whether feeding condition or the reinforcer used to maintain responding impacts the effects of cocaine. Dopamine receptor agonists and antagonists were examined for their ability to mimic or attenuate, respectively, the effects of cocaine. Apomorphine, quinpirole, and lisuride occasioned >90 % responding on the cocaine-associated lever in free-feeding rats responding under a schedule of SST; apomorphine, but not quinpirole or lisuride, occasioned >90 % responding on the cocaine lever in food-restricted rats responding under a schedule of SST. In food-restricted rats responding for food these drugs occasioned little cocaine lever responding and were comparatively more potent in decreasing responding. In free-feeding rats, the effects of cocaine were attenuated by the D2/D3 receptor antagonist raclopride and the D3 receptor-selective antagonist PG01037. In food-restricted rats, raclopride and the D2 receptor-selective antagonist L-741,626 attenuated the effects of cocaine. Raclopride antagonized quinpirole in all groups while PG01037 antagonized quinpirole only in free-feeding rats. These results demonstrate significant differences in the discriminative stimulus of cocaine that are due to feeding conditions and not to the use of different reinforcers across procedures.

**MicroRNA-128 Governs Neuronal Excitability and Motor Behavior In Mice** Tan CL, Plotkin JL, Veno MT, von Schimmelmann M, Feinberg P, Mann S, Handler A, Kjems J, Surmeier DJ, O'Carroll D, Greengard P, Schaefer A. Science. 2013; 342(6163): 1254-1258.

The control of motor behavior in animals and humans requires constant adaptation of neuronal networks to signals of various types and strengths. The authors found that microRNA-128 (miR-128), which is expressed in adult neurons, regulates motor behavior by modulating neuronal signaling networks and excitability. miR-128 governs motor activity by suppressing the expression of various ion channels and signaling components of the extracellular signal-regulated kinase ERK2 network that regulate neuronal excitability. In mice, a reduction of miR-128 expression in postnatal neurons causes increased motor activity and fatal epilepsy. Overexpression of miR-128 attenuates neuronal responsiveness, suppresses motor activity, and alleviates motor abnormalities associated with Parkinson's-like disease and seizures in mice. These data suggest a therapeutic potential for miR-128 in the treatment of epilepsy and movement disorders.

**Cocaine Self-Administration Abolishes Associative Neural Encoding In the Nucleus Accumbens Necessary For Higher-Order Learning** Saddoris MP, Carelli RM. Biol Psychiatry 2014; 75(2): 156-164.

Cocaine use is often associated with diminished cognitive function, persisting even after abstinence from the drug. Likely targets for these changes are the core and shell of the nucleus accumbens (NAc), which are critical for mediating the rewarding aspects of drugs of abuse as well as supporting associative learning. To understand this deficit, the authors recorded neural activity in the NAc of rats with a history of cocaine self-administration or control subjects while they learned Pavlovian first- and second-order associations. Rats were trained for 2 weeks to self-administer intravenous cocaine or water. Later, rats learned a first-order Pavlovian discrimination where a conditioned stimulus (CS)+ predicted food, and a control (CS-) did not. Rats then learned a second-order association where, absent any food reinforcement, a novel cued (SOC+) predicted the CS+ and another (SOC-) predicted the CS-. Electrophysiological recordings were taken during performance of these tasks in the NAc core and shell. Both control subjects and cocaine-experienced rats learned the first-order association, but only control subjects learned the second-order association. Neural recordings indicated that core and shell neurons encoded task-relevant information that correlated with behavioral performance, whereas this type of encoding was abolished in cocaine-experienced rats. The NAc core and shell perform complementary roles in supporting normal associative learning, functions that are impaired after

cocaine experience. This impoverished encoding of motivational behavior, even after abstinence from the drug, might provide a key mechanism to understand why addiction remains a chronically relapsing disorder despite repeated attempts at sobriety.

### **Functional Interaction Between HIV-gp120 and Opioid System in the Preoptic Anterior**

**Hypothalamus** Palma J, Abood ME, Barbe MF, Benamar K. Drug Alcohol Depend 2014; 134: 383-386.

Recently the authors found that fever (part of HIV-related wasting) is induced by the action of the human immunodeficiency virus-1 (HIV-1) envelope glycoprotein (gp120) in the preoptic anterior hypothalamus (POAH). As the opioid system plays a role in the pathogenesis of HIV-1, in the present study the authors sought to examine the capacity of the opioid system to regulate the febrile response induced by gp120. Stainless steel cannulas were stereotactically into the POAH, and a biotelemetry system was used to monitor the body temperature (Tb changes). The authors examined the in vivo effects of naloxone as well as highly opioid-selective receptor antagonists, on gp120-induced fever. Pretreatment with naloxone or the mu-opioid receptor-selective antagonist, cyclic d-Phe-Cys-Tyr-d-Trp-Arg-Thr-Pen-Thr-NH<sub>2</sub> (CTAP), significantly delayed the febrile response induced by gp120. In contrast, naltriben (NTB), a selective antagonist for the delta-2 opioid receptor, did not cause any effect on gp120-induced fever. These results (1) provide pharmacologic evidence of a functional in vivo interaction between the opioid system and this viral protein in the POAH and (2) show that mu-opioid receptors can regulate gp120-induced fever.

### **Hippocampal Long-Term Potentiation Is Disrupted During Expression and Extinction But Is Restored After Reinstatement Of Morphine Place Preference**

Portugal GS, Al-Hasani R, Fakira AK, Gonzalez-Romero JL, Melyan Z, McCall JG, Bruchas MR, Moron JA. J Neurosci 2014; 34(2): 527-538.

Learned associations between environmental cues and morphine use play an important role in the maintenance and/or relapse of opioid addiction. Although previous studies suggest that context-dependent morphine treatment alters glutamatergic transmission and synaptic plasticity in the hippocampus, their role in morphine conditioned place preference (CPP) and reinstatement remains unknown. The authors investigated changes in synaptic plasticity and NMDAR expression in the hippocampus after the expression, extinction, and reinstatement of morphine CPP. Here they report that morphine CPP is associated with increased basal synaptic transmission, impaired hippocampal long-term potentiation (LTP), and increased synaptic expression of the NR1 and NR2b NMDAR subunits. Changes in synaptic plasticity, synaptic NR1 and NR2b expression, and morphine CPP were absent when morphine was not paired with a specific context. Furthermore, hippocampal LTP was impaired and synaptic NR2b expression was increased after extinction of morphine CPP, indicating that these alterations in plasticity may be involved in the mechanisms underlying the learning of drug-environment associations. After extinction of morphine CPP, a priming dose of morphine was sufficient to reinstate morphine CPP and was associated with LTP that was indistinguishable from saline control groups. In contrast, morphine CPP extinguished mice that received a saline priming dose did not show CPP and had disrupted hippocampal LTP. Finally, the authors found that reinstatement of morphine CPP was prevented by the selective blockade of the NR2b subunit in the hippocampus. Together, these data suggest that alterations in synaptic plasticity and glutamatergic transmission play an important role in the reinstatement of morphine CPP.

**Transcriptome-wide Discovery of microRNA Binding Sites in Human Brain** Boudreau RL, Jiang P, Gilmore BL, Spengler RM, Tirabassi R, Nelson JA, Ross CA, Xing Y, Davidson BL. *Neuron*. 2014; 81(2): 294-305.

The orchestration of brain function requires complex gene regulatory networks that are modulated, in part, by microRNAs (miRNAs). These noncoding RNAs associate with argonaute (Ago) proteins in order to direct posttranscriptional gene suppression via base pairing with target transcripts. In order to better understand how miRNAs contribute to human-specialized brain processes and neurological phenotypes, identifying their targets is of paramount importance. Here, the authors address the latter by profiling Ago2:RNA interactions using HITS-CLIP to generate a transcriptome-wide map of miRNA binding sites in human brain. They uncovered ~ 7,000 stringent Ago2 binding sites that are highly enriched for conserved sequences corresponding to abundant brain miRNAs. This interactome points to functional miRNA:target pairs across >3,000 genes and represents a valuable resource for accelerating our understanding of miRNA functions in brain. The authors demonstrate the utility of this map for exploring clinically relevant miRNA binding sites that may facilitate the translation of genetic studies of complex neuropsychiatric diseases into therapeutics.

**Phasic Dopamine Release In the Rat Nucleus Accumbens Symmetrically Encodes A Reward Prediction Error Term** Hart AS, Rutledge RB, Glimcher PW, Phillips PE. *MJ Neurosci* 2014; 34(3): 698-704.

Making predictions about the rewards associated with environmental stimuli and updating those predictions through feedback is an essential aspect of adaptive behavior. Theorists have argued that dopamine encodes a reward prediction error (RPE) signal that is used in such a reinforcement learning process. Recent work with fMRI has demonstrated that the BOLD signal in dopaminergic target areas meets both necessary and sufficient conditions of an axiomatic model of the RPE hypothesis. However, there has been no direct evidence that dopamine release itself also meets necessary and sufficient criteria for encoding an RPE signal. Further, the fact that dopamine neurons have low tonic firing rates that yield a limited dynamic range for encoding negative RPEs has led to significant debate about whether positive and negative prediction errors are encoded on a similar scale. To address both of these issues, the authors used fast-scan cyclic voltammetry to measure reward-evoked dopamine release at carbon fiber electrodes chronically implanted in the nucleus accumbens core of rats trained on a probabilistic decision-making task. They demonstrate that dopamine concentrations transmit a bidirectional RPE signal with symmetrical encoding of positive and negative RPEs. These findings strengthen the case that changes in dopamine concentration alone are sufficient to encode the full range of RPEs necessary for reinforcement learning.

**Identification Of Novel Functionally Selective K-Opioid Receptor Scaffolds** White KL, Scopton AP, Rives ML, Bikbulatov RV, Polepally PR, Brown PJ, Kenakin T, Javitch JA, Zjawiony JK, Roth BL. *Mol Pharmacol* 2014; 85(1): 83-90.

The  $\kappa$ -opioid receptor (KOR)-dynorphin system has been implicated in the control of affect, cognition, and motivation, and is thought to be dysregulated in mood and psychotic disorders, as well as in various phases of opioid dependence. KOR agonists exhibit analgesic effects, although the adverse effects produced by some KOR agonists, including sedation, dysphoria, and hallucinations, have limited their clinical use. Interestingly, KOR-mediated dysphoria, assessed in rodents as aversion, has recently been attributed to the activation of the p38 mitogen-activated protein kinase pathway following arrestin recruitment to the activated KOR. Therefore, KOR-selective G protein-biased agonists, which do not recruit arrestin, have been proposed to be more effective analgesics, without the adverse effects triggered by the arrestin pathway. As an initial step toward identifying novel biased KOR agonists, the authors applied a multifaceted screening strategy utilizing both in silico and parallel

screening approaches. They identified several KOR-selective ligand scaffolds with a range of signaling bias in vitro. The arylacetamide-based scaffold includes both G protein- and  $\beta$ -arrestin-biased ligands, while the endogenous peptides and the diterpene scaffolds are G protein biased. Interestingly, they found scaffold screening to be more successful than library screening in identifying biased ligands. Many of the identified functionally selective ligands are potent selective KOR agonists that are reported to be active in the central nervous system. They therefore represent excellent candidates for in vivo studies aiming at determining the behavioral effects mediated by specific KOR-mediated signaling cascades.

### **Disruption Of Glutamate Receptor-Interacting Protein In Nucleus Accumbens Enhances**

**Vulnerability To Cocaine Relapse** Briand LA, Kimmey BA, Ortinski PI, Haganir RL, Pierce RC. Neuropsychopharmacology 2014; 39(3): 759-769.

Trafficking and stabilization of AMPA receptors at synapses in response to cocaine exposure is thought to be critical for expression of cocaine addiction and relapse. Glutamate receptor-interacting protein (GRIP) is a neuronal scaffolding protein that stabilizes GluA2 AMPARs at synapses but its role in cocaine addiction has not been examined. The current study demonstrates that conditional deletion of GRIP within the nucleus accumbens potentiates cue-induced reinstatement of cocaine seeking without affecting operant learning, locomotor activity, or reinstatement of natural reward seeking. This is the first study to demonstrate a role for accumbal GRIP in behavior.

Electrophysiological recordings revealed increased rectification of AMPAR-mediated currents in the nucleus accumbens and increased AMPAR sensitivity to the GluA2-lacking AMPAR antagonist, 1-naphthylacetyl spermine, indicative of an increased contribution of GluA2-lacking calcium-permeable AMPARs. In addition, accumbal GRIP deletion was associated with blunted long-term depression, similar to what is seen following cocaine self-administration. Taken together, these results indicate that GRIP may modulate addictive phenotypes through its regulation of synaptic AMPARs by controlling their subunit composition and susceptibility to LTD. These effects are associated with changes in vulnerability to cocaine relapse and highlight GRIP as a novel target for the development of cocaine addiction therapeutics.

### **Whole-Brain Circuit Dissection In Free-Moving Animals Reveals Cell-Specific**

**Mesocorticolimbic Networks** Michaelides M, Anderson SAR, Ananth M, Smirnov D, Thanos PK, Neumaier JF, Wang GJ, Volkow ND, Hurd YL. J Clin Invest 2013; 123(12): 5342-5350.

The ability to map the functional connectivity of discrete cell types in the intact mammalian brain during behavior is crucial for advancing our understanding of brain function in normal and disease states. The authors combined designer receptor exclusively activated by designer drug (DREADD) technology and behavioral imaging with  $\mu$ PET and [ $^{18}$ F]fluorodeoxyglucose (FDG) to generate whole-brain metabolic maps of cell-specific functional circuits during the awake, freely moving state. The authors have termed this approach DREADD-assisted metabolic mapping (DREAMM) and documented its ability in rats to map whole-brain functional anatomy. They applied this strategy to evaluating changes in the brain associated with inhibition of prodynorphin-expressing (Pdyn-expressing) and of proenkephalin-expressing (Penk-expressing) medium spiny neurons (MSNs) of the nucleus accumbens shell (NAcSh), which have been implicated in neuropsychiatric disorders. DREAMM revealed discrete behavioral manifestations and concurrent engagement of distinct corticolimbic networks associated with dysregulation of Pdyn and Penk in MSNs of the NAcSh. Furthermore, distinct neuronal networks were recruited in awake versus anesthetized conditions. These data demonstrate that DREAMM is a highly sensitive, molecular, high-resolution quantitative imaging approach.

**Optogenetic Identification Of An Intrinsic Cholinergically Driven Inhibitory Oscillator Sensitive To Cannabinoids and Opioids In Hippocampal CA1** Nagode DA, Tang AH, Yang K, Alger BE. J Physiol 2014; 592(Pt 1): 103-123.

Neuronal electrical oscillations in the theta (4-14 Hz) and gamma (30-80 Hz) ranges are necessary for the performance of certain animal behaviours and cognitive processes. Perisomatic GABAergic inhibition is prominently involved in cortical oscillations driven by ACh release from septal cholinergic afferents. In neocortex and hippocampal CA3 regions, parvalbumin (PV)-expressing basket cells, activated by ACh and glutamatergic agonists, largely mediate oscillations. However, in CA1 hippocampus in vitro, cholinergic agonists or the optogenetic release of endogenous ACh from septal afferents induces rhythmic, theta-frequency inhibitory postsynaptic currents (IPSCs) in pyramidal cells, even with glutamatergic transmission blocked. The IPSCs are regulated by exogenous and endogenous cannabinoids, suggesting that they arise from type 1 cannabinoid receptor-expressing (CB1R+) interneurons - mainly cholecystokinin (CCK)-expressing cells. Nevertheless, an occult contribution of PV-expressing interneurons to these rhythms remained conceivable. Here, the authors directly test this hypothesis by selectively silencing CA1 PV-expressing cells optogenetically with halorhodopsin or archaerhodopsin. However, this had no effect on theta-frequency IPSC rhythms induced by carbachol (CCh). In contrast, the silencing of glutamic acid decarboxylase 2-positive interneurons, which include the CCK-expressing basket cells, strongly suppressed inhibitory oscillations; PV-expressing interneurons appear to play no role. The low-frequency IPSC oscillations induced by CCh or optogenetically stimulated ACh release were also inhibited by a  $\mu$ -opioid receptor (MOR) agonist, which was unexpected because MORs in CA1 are not usually associated with CCK-expressing cells. These results reveal novel properties of an inhibitory oscillator circuit within CA1 that is activated by muscarinic agonists. The oscillations could contribute to behaviourally relevant, atropine-sensitive, theta rhythms and link cannabinoid and opioid actions functionally.

**Effects of Chronic Varenicline Treatment On Nicotine, Cocaine, and Concurrent Nicotine+Cocaine Self-Administration** Mello NK, Fivel PA, Kohut SJ, Carroll FI. Neuropsychopharmacology. 2014 Apr; 39(5): 1222-1231.

Nicotine dependence and cocaine abuse are major public health problems, and most cocaine abusers also smoke cigarettes. An ideal treatment medication would reduce both cigarette smoking and cocaine abuse. Varenicline is a clinically available, partial agonist at  $\alpha 4\beta 2^*$  and  $\alpha 6\beta 2^*$  nicotinic acetylcholine receptors (nAChRs) and a full agonist at  $\alpha 7$  nAChRs. Varenicline facilitates smoking cessation in clinical studies and reduced nicotine self-administration, and substituted for the nicotine-discriminative stimulus in preclinical studies. The present study examined the effects of chronic varenicline treatment on self-administration of IV nicotine, IV cocaine, IV nicotine+cocaine combinations, and concurrent food-maintained responding by five cocaine- and nicotine-experienced adult rhesus monkeys (*Macaca mulatta*). Varenicline (0.004-0.04 mg/kg/h) was administered intravenously every 20 min for 23 h each day for 7-10 consecutive days. Each varenicline treatment was followed by saline-control treatment until food- and drug-maintained responding returned to baseline. During control treatment, nicotine+cocaine combinations maintained significantly higher levels of drug self-administration than nicotine or cocaine alone ( $P < 0.05$ -0.001). Varenicline dose-dependently reduced responding maintained by nicotine alone (0.0032 mg/kg/inj) ( $P < 0.05$ ), and in combination with cocaine (0.0032 mg/kg/inj) ( $P < 0.05$ ) with no significant effects on food-maintained responding. However, varenicline did not significantly decrease self-administration of a low dose of nicotine (0.001 mg/kg), cocaine alone (0.0032 and 0.01 mg/kg/inj), or 0.01 mg/kg cocaine combined with the same doses of nicotine. The authors conclude that varenicline selectively attenuates the reinforcing effects of nicotine

alone but not cocaine alone, and its effects on nicotine+cocaine combinations are dependent on the dose of cocaine.

**Modelling Individual Differences In the Form Of Pavlovian Conditioned Approach Responses: A Dual Learning Systems Approach With Factored Representations** Lesaint F, Sigaud O, Flagel SB, Robinson TE, Khamassi M. PLoS Comput Biol 2014; 10(2): e1003466.

Reinforcement learning has greatly influenced models of conditioning, providing powerful explanations of acquired behaviour and underlying physiological observations. However, in recent autoshaping experiments in rats, variation in the form of Pavlovian conditioned responses (CRs) and associated dopamine activity, have questioned the classical hypothesis that phasic dopamine activity corresponds to a reward prediction error-like signal arising from a classical Model-Free system, necessary for Pavlovian conditioning. Over the course of Pavlovian conditioning using food as the unconditioned stimulus (US), some rats (sign-trackers) come to approach and engage the conditioned stimulus (CS) itself - a lever - more and more avidly, whereas other rats (goal-trackers) learn to approach the location of food delivery upon CS presentation. Importantly, although both sign-trackers and goal-trackers learn the CS-US association equally well, only in sign-trackers does phasic dopamine activity show classical reward prediction error-like bursts. Furthermore, neither the acquisition nor the expression of a goal-tracking CR is dopamine-dependent. Here the authors present a computational model that can account for such individual variations. They show that a combination of a Model-Based system and a revised Model-Free system can account for the development of distinct CRs in rats. Moreover, they show that revising a classical Model-Free system to individually process stimuli by using factored representations can explain why classical dopaminergic patterns may be observed for some rats and not for others depending on the CR they develop. In addition, the model can account for other behavioural and pharmacological results obtained using the same, or similar, autoshaping procedures. Finally, the model makes it possible to draw a set of experimental predictions that may be verified in a modified experimental protocol. The authors suggest that further investigation of factored representations in computational neuroscience studies may be useful.

**TGF- $\beta$  Signaling Regulates Neuronal C1q Expression and Developmental Synaptic Refinement** Bialas AR, Stevens B. Nat Neurosci 2013; 16(12): 1773-1782.

Immune molecules, including complement proteins C1q and C3, have emerged as critical mediators of synaptic refinement and plasticity. Complement localizes to synapses and refines the developing visual system through C3-dependent microglial phagocytosis of synapses. Retinal ganglion cells (RGCs) express C1q, the initiating protein of the classical complement cascade, during retinogeniculate refinement; however, the signals controlling C1q expression and function remain elusive. Previous work implicated an astrocyte-derived factor in regulating neuronal C1q expression. Here the authors identify retinal transforming growth factor (TGF)- $\beta$  as a key regulator of neuronal C1q expression and synaptic pruning in the developing visual system. Mice lacking TGF- $\beta$  receptor II (TGF $\beta$ RII) in retinal neurons had reduced C1q expression in RGCs and reduced synaptic localization of complement, and phenocopied refinement defects observed in complement-deficient mice, including reduced eye-specific segregation and microglial engulfment of RGC inputs. These data implicate TGF- $\beta$  in regulating neuronal C1q expression to initiate complement- and microglia-mediated synaptic pruning.

**Low- and High-Cocaine Locomotor Responding Rats Differ In Reinstatement Of Cocaine Seeking and Striatal mGluR5 Protein Expression** Simmons DL, Mandt BH, Ng CMC, Richards TL, Yamamoto DJ, Zahniser NR, Allen RM. Neuropharmacology 2013; 75: 347-355.

Behavioral responsiveness to initial cocaine use varies among individuals and may contribute to differential vulnerability to cocaine addiction. Rats also exhibit individual differences in cocaine's

effects and can be classified as low or high cocaine responders (LCRs or HCRs, respectively), based on their initial cocaine-induced locomotor activity (10 mg/kg, i.p.). Here, the authors used the extinction/reinstatement model to address whether or not LCRs and HCRs differ in (i) extinction/reinstatement of cocaine self-administration behavior and (ii) levels of metabotropic glutamate receptors (mGluRs) following these behaviors. During the earliest acquisition sessions, LCRs exhibited significantly greater cocaine intake (0.8 mg/kg/infusion) and cocaine-paired lever responding than HCRs, but intake and lever responding converged by the end of the cocaine self-administration portion of the study. LCRs and HCRs did not differ in cocaine seeking during the first extinction session and extinguished cocaine seeking similarly. HCRs exhibited greater reinstatement than LCRs to lower (2.5 and 5 mg/kg), but not higher (10 mg/kg), i.p. priming doses of cocaine. The effect of drug-paired cues on reinstatement following extinction was complex, with HCRs and LCRs showing the greater effect of cue depending on the order in which cue- and drug-primed tests were given. Western blot analysis revealed that mGluR5 heteromers were significantly higher in the dorsal striatum of HCRs than LCRs following reinstatement testing. Although the authors' previous findings with the LCR/HCR model have uniformly supported the idea that lower initial cocaine-induced activation predicts more ready development of cocaine addiction-like behaviors, here, they show a more complex relationship with cocaine reinstatement.

#### **Target-Selective Phototherapy Using a Ligand-Based Photosensitizer for Type 2 Cannabinoid**

**Receptor** Zhang S, Jia N, Shao P, Tong Q, Xi XQ, Bai M. Chem Biol 2014 Mar 20; 21(3): 338-344. Phototherapy is a powerful, noninvasive approach for cancer treatment, with several agents currently in clinical use. Despite the progress and promise, most current phototherapy agents have serious side effects as they can lead to damage to healthy tissue, even when the photosensitizers are fused to targeting molecules due to nonspecific light activation of the unbound photosensitizer. To overcome these limitations, the authors developed a phototherapy agent that combines a functional ligand and a near infrared phthalocyanine dye. Their target is type 2 cannabinoid receptor (CB2R), considered an attractive therapeutic target for phototherapy given it is overexpressed by many types of cancers that are located at a surface or can be reached by an endoscope. They show that their CB2R-targeted phototherapy agent, IR700DX-mbc94, is specific for CB2R and effective only when bound to the target receptor. Overall, this opens up the opportunity for development of an alternative treatment option for CB2R-positive cancers.

#### **Low Frequency Repetitive Transcranial Magnetic Stimulation Of the Left Dorsolateral Prefrontal Cortex Transiently Increases Cue-Induced Craving For Methamphetamine: A**

**Preliminary Study** Li X, Malcolm RJ, Huebner K, Hanlon CA, Taylor JJ, Brady KT, George MS, See RE. Drug Alcohol Depend 2013; 133(2): 641-646.

Repetitive transcranial magnetic stimulation (rTMS) can temporarily interrupt or facilitate activity in a focal brain region. Several lines of evidence suggest that rTMS of the dorsolateral prefrontal cortex (DLPFC) can affect processes involved in drug addiction. The authors hypothesized that a single session of low-frequency rTMS of the left DLPFC would modulate cue-induced craving for methamphetamine (MA) when compared to a sham rTMS session. In this single-blind, sham-controlled crossover study, 10 non-treatment seeking MA-dependent users and 8 healthy controls were randomized to receive 15 min of sham and real (1 Hz) DLPFC rTMS in two experimental sessions separated by 1h. During each rTMS session, participants were exposed to blocks of neutral cues and MA-associated cues. Participants rated their craving after each cue block. In MA users, real rTMS over the left DLPFC increased self-reported craving as compared to sham stimulation ( $17.86 \pm 1.46$  vs.  $24.85 \pm 1.57$ ,  $p=0.001$ ). rTMS had no effect on craving in healthy controls. One Hertz rTMS of the left DLPFC was safe and tolerable for all participants. Low frequency rTMS of the left DLPFC transiently

increased cue-induced craving in MA participants. These preliminary results suggest that 1 Hz rTMS of the left DLPFC may increase craving by inhibiting the prefrontal cortex or indirectly activating subcortical regions involved in craving.

**Genetic and Pharmacokinetic Determinants Of Response To Transdermal Nicotine In White, Black, and Asian Nonsmokers** Dempsey DA, St Helen G, Jacob 3rd P, Tyndale RF, Benowitz NL. Clin Pharmacol Ther 2013; 94(6): 687-694.

The aim of the study was to examine genetic, pharmacokinetic, and demographic factors that influence sensitivity to nicotine in never-smokers. Sixty never-smokers, balanced for gender and race (white, black, and Asian), wore 7-mg nicotine skin patches for up to 8 h. Serial plasma nicotine concentrations and subjective and cardiovascular effects were measured, and genetic variation in the CYP2A6 gene, encoding the primary enzyme responsible for nicotine metabolism, was assessed. Nicotine toxicity requiring patch removal developed in nine subjects and was strongly associated with rate of increase and peak concentrations of plasma nicotine. Toxicity and subjective and cardiovascular effects of nicotine were associated with the presence of reduced-function CYP2A6 alleles, presumably reflecting slow nicotine metabolic inactivation. This study has implications for understanding individual differences in responses to nicotine medications, particularly when they are used for treating medical conditions in nonsmokers, and possibly in vulnerability to developing nicotine dependence.

**Design, Synthesis, and Characterization of  $\alpha$ -Ketoheterocycles That Additionally Target the Cytosolic Port Cys269 of Fatty Acid Amide Hydrolase** Otrubova K, Cravatt BF, Boger DL. J Med Chem 2014; 57(3): 1079-1089.

A series of  $\alpha$ -ketooxazoles incorporating electrophiles at the C5 position of the pyridyl ring of 2 (OL-135) and related compounds were prepared and examined as inhibitors of fatty acid amide hydrolase (FAAH) that additionally target the cytosolic port Cys269. From this series, a subset of the candidate inhibitors exhibited time-dependent FAAH inhibition and noncompetitive irreversible inactivation of the enzyme, consistent with the targeted Cys269 covalent alkylation or addition, and maintained or enhanced the intrinsic selectivity for FAAH versus other serine hydrolases. A preliminary in vivo assessment demonstrates that these inhibitors raise endogenous brain levels of anandamide and other FAAH substrates upon intraperitoneal (i.p.) administration to mice, with peak levels achieved within 1.5-3 h, and that the elevations of the signaling lipids were maintained >6 h, indicating that the inhibitors effectively reach and remain active in the brain, inhibiting FAAH for a sustained period.

**Adolescent Risk Taking, Cocaine Self-Administration, and Striatal Dopamine Signaling.** Mitchell MR, Weiss VG, Beas BS, Morgan D, Bizon JL, Setlow B. Neuropsychopharmacology 2014; 39(4): 955-962.

Poor decision making and elevated risk taking, particularly during adolescence, have been strongly linked to drug use; however the causal relationships among these factors are not well understood. To address these relationships, a rat model (the Risky Decision-making Task; RDT) was used to determine whether individual differences in risk taking during adolescence predict later propensity for cocaine self-administration and/or whether cocaine self-administration causes alterations in risk taking. In addition, the RDT was used to determine how risk taking is modulated by dopamine signaling, particularly in the striatum. Results from these experiments indicated that greater risk taking during adolescence predicted greater intake of cocaine during acquisition of self-administration in adulthood, and that adult cocaine self-administration in turn caused elevated risk taking that was present following 6 weeks of abstinence. Greater adolescent risk taking was associated with lower striatal D2 receptor mRNA expression, and pharmacological activation of D2/3 receptors in the ventral, but not dorsal, striatum induced a decrease in risk taking. These findings indicate that the relationship between



elevated risk taking and cocaine self-administration is bi-directional, and that low striatal D2 receptor expression may represent a predisposing factor for both maladaptive decision making and cocaine use. Furthermore, these findings suggest that striatal D2 receptors represent a therapeutic target for attenuating maladaptive decision making when choices include risk of adverse consequences.

### **Propensity For Social Interaction Predicts Nicotine-Reinforced Behaviors In Outbred Rats**

Wang T, Han W, Wang B, Jiang Q, Solberg-Woods LC, Palmer AA, Chen H. *Genes Brain Behav* 2014; 13(2): 202-212.

Social and genetic factors can influence smoking behavior. Using olfactogustatory stimuli as the sensory cue for intravenous nicotine self-administration (SA), the authors previously showed that social learning of nicotine contingent odor cue prevented rats from developing conditioned taste aversion and allowed them to instead establish stable nicotine SA. They hypothesized that genetic factors influenced socially acquired nicotine SA. A heterogeneous stock (HS; N/NIH) of outbred rats was trained to self-administer nicotine using the social learning protocol. Both male and female HS rats acquired nicotine SA, but females self-administered more nicotine than males. After extinction, the context previously paired with nicotine SA, in conjunction with socially transmitted drug cues, was sufficient to cause reinstatement of drug-seeking behavior. Wide variation in both nicotine intake and reinstatement was observed. Using multiple regression analysis, they found that measures of social interaction were significant predictors of nicotine intake and reinstatement of drug seeking in both males and females. Furthermore, measures of depression were predictors of nicotine intake in both males and females, anxiety was a predictor only in males and response to novelty was a predictor only in females. In males, measures of both depression and anxiety predicted nicotine reinstatement. Together, these data supported the ideas that genetically determined propensities for emotional and social phenotypes are significant determinants for nicotine-reinforced behavior, and that the HS rat is a suitable tool for dissecting genetic mechanisms that may underlie the interaction between social behavior, anxiety, depression and smoking.

### **Two Novel Mutations In ABHD12: Expansion Of the Mutation Spectrum In PHARC and Assessment Of Their Functional Effects**

Chen DH, Naydenov A, Blankman JL, Mefford HC, Davis M, Sul Y, Barloon AS, Bonkowski E, Wolff J, Matsushita M, Smith C, Cravatt BF, Mackie K, Raskind WH, Stella N, Bird TD. *Hum Mutat* 2013; 34(12): 1672-1678.

PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataracts) is a recently described autosomal-recessive neurodegenerative disease caused by mutations in the  $\alpha$ - $\beta$ -hydrolase domain-containing 12 gene (ABHD12). Only five homozygous ABHD12 mutations have been reported and the pathogenesis of PHARC remains unclear. The authors evaluated a woman who manifested short stature as well as the typical features of PHARC. Sequence analysis of ABHD12 revealed a novel heterozygous c.1129A>T (p.Lys377\*) mutation. Targeted comparative genomic hybridization detected a 59-kb deletion that encompasses exon 1 of ABHD12 and exons 1-4 of an adjacent gene, GINS1, and includes the promoters of both genes. The heterozygous deletion was also carried by the patient's asymptomatic mother. Quantitative reverse transcription-PCR demonstrated ~50% decreased expression of ABHD12 RNA in lymphoblastoid cell lines from both individuals. Activity-based protein profiling of serine hydrolases revealed absence of ABHD12 hydrolase activity in the patient and 50% reduction in her mother. This is the first report of compound heterozygosity in PHARC and the first study to describe how a mutation might affect ABHD12 expression and function. The possible involvement of haploinsufficiency for GINS1, a DNA replication complex protein, in the short stature of the patient and her mother requires further studies.

**Exposure To Nicotine Enhances Its Subsequent Self-Administration: Contribution Of Nicotine-Associated Contextual Stimuli** Neugebauer NM, Cortright JJ, Sampedro GR, Vezina P. Behav Brain Res 2014; 260: 155-161.

Contextual stimuli present during nicotine exposure can come to act as conditioned stimuli and have been shown to play an important role in ongoing nicotine self-administration. In the present study, the authors characterized the effects of contextual stimuli previously paired with non-contingent nicotine exposure injections on subsequent nicotine self-administration. Rats were exposed to five injections of either saline or nicotine (0.4 mg/kg, i.p.) in either their home cage or a self-administration chamber with the levers retracted. Two weeks later, they were allowed to self-administer nicotine (30 µg/kg/infusion, IV) under fixed ratio (FR) schedules of reinforcement across 12 consecutive sessions. Lastly, responding under a progressive ratio (PR) schedule was assessed. Rats exposed to nicotine in the self-administration chamber subsequently increased their intake of nicotine across the FR test days, obtaining more infusions on average by days 7-12 compared to their saline exposed controls. This increase was not due to nicotine exposure alone as rats exposed to nicotine in the home cage did not show this effect. It was also not due to differences in the final ratio achieved between nicotine and saline exposed rats. Although rats exposed to nicotine in the self-administration chambers displayed reduced discrimination between the active and inactive levers during FR testing, they showed increased motivation to self-administer nicotine under the PR schedule. These results indicate that exposure to nicotine can enhance its subsequent self-administration and highlight the contribution of nicotine-associated contextual stimuli to the work output rats ultimately emit to obtain the drug.

**Cell Death By Pyroptosis Drives CD4 T-Cell Depletion In HIV-1 Infection** Doitsh G, Galloway NLK, Geng X, Yang Z, Monroe KM, Zepeda O, Hunt PW, Hatano H, Sowinski S, Munoz-Arias I, Greene WC. Nature 2014; 505(7484): 509-514.

The pathway causing CD4 T-cell death in HIV-infected hosts remains poorly understood although apoptosis has been proposed as a key mechanism. The authors now show that caspase-3-mediated apoptosis accounts for the death of only a small fraction of CD4 T cells corresponding to those that are both activated and productively infected. The remaining over 95% of quiescent lymphoid CD4 T cells die by caspase-1-mediated pyroptosis triggered by abortive viral infection. Pyroptosis corresponds to an intensely inflammatory form of programmed cell death in which cytoplasmic contents and pro-inflammatory cytokines, including IL-1 $\beta$ , are released. This death pathway thus links the two signature events in HIV infection-CD4 T-cell depletion and chronic inflammation-and creates a pathogenic vicious cycle in which dying CD4 T cells release inflammatory signals that attract more cells to die. This cycle can be broken by caspase 1 inhibitors shown to be safe in humans, raising the possibility of a new class of 'anti-AIDS' therapeutics targeting the host rather than the virus.

**Molecular Control Of  $\Delta$ -Opioid Receptor Signalling** Fenalti G, Giguere PM, Katritch V, Huang XP, Thompson AA, Cherezov V, Roth BL, Stevens RC. Nature 2014; 506(7487): 191-196.

Opioids represent widely prescribed and abused medications, although their signal transduction mechanisms are not well understood. Here the authors present the 1.8 Å high-resolution crystal structure of the human  $\delta$ -opioid receptor ( $\delta$ -OR), revealing the presence and fundamental role of a sodium ion in mediating allosteric control of receptor functional selectivity and constitutive activity. The distinctive  $\delta$ -OR sodium ion site architecture is centrally located in a polar interaction network in the seven-transmembrane bundle core, with the sodium ion stabilizing a reduced agonist affinity state, and thereby modulating signal transduction. Site-directed mutagenesis and functional studies reveal that changing the allosteric sodium site residue Asn 131 to an alanine or a valine augments constitutive  $\beta$ -arrestin-mediated signalling. Asp95Ala, Asn310Ala and Asn314Ala mutations transform classical  $\delta$ -opioid antagonists such as naltrindole into potent  $\beta$ -arrestin-biased agonists. The data establish the

molecular basis for allosteric sodium ion control in opioid signalling, revealing that sodium-coordinating residues act as 'efficacy switches' at a prototypic G-protein-coupled receptor.

**Multilevel Modulation Of A Sensory Motor Circuit During C. Elegans Sleep and Arousal** Cho JY, Sternberg PW. Cell 2014; 156(1-2): 249-260.

Sleep is characterized by behavioral quiescence, homeostasis, increased arousal threshold, and rapid reversibility. Understanding how these properties are encoded by a neuronal circuit has been difficult, and no single molecular or neuronal pathway has been shown to be responsible for the regulation of sleep. Taking advantage of the well-mapped neuronal connections of *Caenorhabditis elegans* and the sleep-like states in this animal, the authors demonstrate the changed properties of both sensory neurons and downstream interneurons that mediate sleep and arousal. The ASH sensory neuron displays reduced sensitivity to stimuli in the sleep-like state, and the activity of the corresponding interneurons in ASH's motor circuit becomes asynchronous. Restoration of interneuron synchrony is sufficient for arousal. The multilevel circuit depression revealed provides an elegant strategy to promote a robust decrease in arousal while allowing for rapid reversibility of the sleep state.

**Tachykinin-Expressing Neurons Control Male-Specific Aggressive Arousal In Drosophila**

Asahina K, Watanabe K, Duistermars BJ, Hoopfer E, Gonzalez CR, Eyjolfsson EA, Perona P, Anderson DJ. Cell 2014; 156(1-2): 221-235.

Males of most species are more aggressive than females, but the neural mechanisms underlying this dimorphism are not clear. Here, the authors identify a neuron and a gene that control the higher level of aggression characteristic of *Drosophila melanogaster* males. Males, but not females, contain a small cluster of FruM(+) neurons that express the neuropeptide tachykinin (Tk). Activation and silencing of these neurons increased and decreased, respectively, intermale aggression without affecting male-female courtship behavior. Mutations in both Tk and a candidate receptor, *Takr86C*, suppressed the effect of neuronal activation, whereas overexpression of Tk potentiated it. Tk neuron activation overcame reduced aggressiveness caused by eliminating a variety of sensory or contextual cues, suggesting that it promotes aggressive arousal or motivation. Tachykinin/Substance P has been implicated in aggression in mammals, including humans. Thus, the higher aggressiveness of *Drosophila* males reflects the sexually dimorphic expression of a neuropeptide that controls agonistic behaviors across phylogeny.

**Long-Acting Integrase Inhibitor Protects Macaques From Intrarectal Simian/Human**

**Immunodeficiency Virus** Andrews CD, Spreen WR, Mohri H, Moss L, Ford S, Gettie A, Russell-Lodrigue K, Bohm RP, Cheng-Mayer C, Hong Z, Markowitz M, Ho DD. Science. 2014; 343(6175): 1151-1154.

GSK1265744 (GSK744) is an integrase strand-transfer inhibitor that has been formulated as a long-acting (LA) injectable suitable for monthly to quarterly clinical administration. GSK744 LA was administered at two time points 4 weeks apart beginning 1 week before virus administration, and macaques were challenged weekly for 8 weeks. GSK744 LA, at plasma concentrations achievable with quarterly injections in humans, protected all animals against repeated low-dose challenges. In a second experiment, macaques were given GSK744 LA 1 week before virus administration and challenged repeatedly until infection occurred. Protection decreased over time and correlated with the plasma drug levels. With a quarterly dosing schedule in humans, these results suggest that GSK744 LA could potentially decrease adherence problems associated with daily preexposure prophylaxis (PrEP).

**IFI16 DNA Sensor Is Required For Death Of Lymphoid CD4 T Cells Abortively Infected With HIV** Monroe KM, Yang Z, Johnson JR, Geng X, Doitsh G, Krogan NJ, Greene WC. Science. 2014; 343(6169): 428-432.

The progressive depletion of quiescent "bystander" CD4 T cells, which are nonpermissive to HIV infection, is a principal driver of the acquired immunodeficiency syndrome (AIDS). These cells undergo abortive infection characterized by the cytosolic accumulation of incomplete HIV reverse transcripts. These viral DNAs are sensed by an unidentified host sensor that triggers an innate immune response, leading to caspase-1 activation and pyroptosis. Using unbiased proteomic and targeted biochemical approaches, as well as two independent methods of lentiviral short hairpin RNA-mediated gene knockdown in primary CD4 T cells, the authors identify interferon- $\gamma$ -inducible protein 16 (IFI16) as a host DNA sensor required for CD4 T cell death due to abortive HIV infection. These findings provide insights into a key host pathway that plays a central role in CD4 T cell depletion during disease progression to AIDS.

**C57BL/6N Mutation In Cytoplasmic FMRP Interacting Protein 2 Regulates Cocaine Response**

Kumar V, Kim K, Joseph C, Kourrich S, Yoo SH, Huang HC, Vitaterna MH, de Villena FPM, Churchill G, Bonci A, Takahashi JS. Science 2013; 342(6165): 1508-1512.

The inbred mouse C57BL/6J is the reference strain for genome sequence and for most behavioral and physiological phenotypes. However, the International Knockout Mouse Consortium uses an embryonic stem cell line derived from a related C57BL/6N substrain. The authors found that C57BL/6N has a lower acute and sensitized response to cocaine and methamphetamine. They mapped a single causative locus and identified a nonsynonymous mutation of serine to phenylalanine (S968F) in Cytoplasmic FMRP interacting protein 2 (Cyfip2) as the causative variant. The S968F mutation destabilizes CYFIP2, and deletion of the C57BL/6N mutant allele leads to acute and sensitized cocaine-response phenotypes. The authors propose that CYFIP2 is a key regulator of cocaine response in mammals and present a framework to use mouse substrains to identify previously unknown genes and alleles regulating behavior.

**Independent Optical Excitation Of Distinct Neural Populations** Klapoetke NC, Murata Y, Kim SS, Pulver SR, Birdsey-Benson A, Cho YK, Morimoto TK, Chuong AS, Carpenter EJ, Tian Z, Wang J, Xie Y, Yan Z, Zhang Y, Chow BY, Surek B, Melkonian M, Jayaraman V, Constantine-Paton M, Wong GKS, Boyden ES. Nat Methods. 2014; 11(3): 338-346.

Optogenetic tools enable examination of how specific cell types contribute to brain circuit functions. A long-standing question is whether it is possible to independently activate two distinct neural populations in mammalian brain tissue. Such a capability would enable the study of how different synapses or pathways interact to encode information in the brain. Here the authors describe two channelrhodopsins, Chronos and Chrimson, discovered through sequencing and physiological characterization of opsins from over 100 species of alga. Chrimson's excitation spectrum is red shifted by 45 nm relative to previous channelrhodopsins and can enable experiments in which red light is preferred. The authors show minimal visual system-mediated behavioral interference when using Chrimson in neurobehavioral studies in *Drosophila melanogaster*. Chronos has faster kinetics than previous channelrhodopsins yet is effectively more light sensitive. Together these two reagents enable two-color activation of neural spiking and downstream synaptic transmission in independent neural populations without detectable cross-talk in mouse brain slice.

**Psychostimulants and Cognition: A Continuum Of Behavioral and Cognitive Activation** Wood S, Sage JR, Shuman T, Anagnostaras SG. Pharmacol Rev 2014; 66(1): 193-221.

Psychostimulants such as cocaine have been used as performance enhancers throughout recorded history. Although psychostimulants are commonly prescribed to improve attention and cognition, a great deal of literature has described their ability to induce cognitive deficits, as well as addiction. How can a single drug class be known to produce both cognitive enhancement and impairment? Properties of the particular stimulant drug itself and individual differences between users have both been suggested to dictate the outcome of stimulant use. A more parsimonious alternative, which we endorse, is that dose is the critical determining factor in cognitive effects of stimulant drugs. Herein, the authors review several popular stimulants (cocaine, amphetamine, methylphenidate, modafinil, and caffeine), outlining their history of use, mechanism of action, and use and abuse today. One common graphic depiction of the cognitive effects of psychostimulants is an inverted U-shaped dose-effect curve. Moderate arousal is beneficial to cognition, whereas too much activation leads to cognitive impairment. In parallel to this schematic, the authors propose a continuum of psychostimulant activation that covers the transition from one drug effect to another as stimulant intake is increased. Low doses of stimulants effect increased arousal, attention, and cognitive enhancement; moderate doses can lead to feelings of euphoria and power, as well as addiction and cognitive impairment; and very high doses lead to psychosis and circulatory collapse. This continuum helps account for the seemingly disparate effects of stimulant drugs, with the same drug being associated with cognitive enhancement and impairment.

**Molecular Mechanisms For Synchronous, Asynchronous, and Spontaneous Neurotransmitter Release** Kaeser PS, Regehr WG. Annu Rev Physiol 2014; 76: 333-363.

Most neuronal communication relies upon the synchronous release of neurotransmitters, which occurs through synaptic vesicle exocytosis triggered by action potential invasion of a presynaptic bouton. However, neurotransmitters are also released asynchronously with a longer, variable delay following an action potential or spontaneously in the absence of action potentials. A compelling body of research has identified roles and mechanisms for synchronous release, but asynchronous release and spontaneous release are less well understood. In this review, we analyze how the mechanisms of the three release modes overlap and what molecular pathways underlie asynchronous and spontaneous release. The authors conclude that the modes of release have key fusion processes in common but may differ in the source of and necessity for  $\text{Ca}^{2+}$  to trigger release and in the identity of the  $\text{Ca}^{2+}$  sensor for release.

**GENSAT BAC Cre-Recombinase Driver Lines To Study The Functional Organization Of Cerebral Cortical and Basal Ganglia Circuits** Gerfen CR, Paletzki R, Heintz N. Neuron 2013; 80(6): 1368-1383.

Recent development of molecular genetic techniques are rapidly advancing understanding of the functional role of brain circuits in behavior. Critical to this approach is the ability to target specific neuron populations and circuits. The collection of over 250 BAC Cre-recombinase driver lines produced by the GENSAT project provides a resource for such studies. Here the authors provide characterization of GENSAT BAC-Cre driver lines with expression in specific neuroanatomical pathways within the cerebral cortex and basal ganglia.

**Causal Evidence Of Performance Monitoring By Neurons In Posterior Cingulate Cortex During Learning** Heilbronner SR, Platt ML. Neuron 2013; 80(6): 1384-1391.

The posterior cingulate cortex (CGp) is a major hub of the default mode network (DMN), a set of cortical areas with high resting activity that declines during task performance. This relationship

suggests that DMN activity contributes to mental processes that are antagonistic to performance. Alternatively, DMN may detect conditions under which performance is poor and marshal cognitive resources for improvement. To test this idea, the authors recorded activity of CGp neurons in monkeys performing a learning task while varying reward size and novelty. They found that CGp neurons responded to errors, and this activity was magnified by small reward and novel stimuli. Inactivating CGp with muscimol impaired new learning when rewards were small but had no effect when rewards were large; inactivation did not affect performance on well-learned associations. Thus, CGp, and by extension the DMN, may support learning, and possibly other cognitive processes, by monitoring performance and motivating exploration.

**Neuronal Origins Of Choice Variability In Economic Decisions** Padoa-Schioppa C. Neuron. 2013; 80(5): 1322-1336.

To investigate the mechanisms through which economic decisions are formed, the author examined the activity of neurons in the orbitofrontal cortex while monkeys chose between different juice types. Different classes of cells encoded the value of individual offers (offer value), the value of the chosen option (chosen value), or the identity of the chosen juice (chosen juice). Choice variability was partly explained by the tendency to repeat choices (choice hysteresis). Surprisingly, near-indifference decisions did not reflect fluctuations in the activity of offer value cells. In contrast, near-indifference decisions correlated with fluctuations in the preoffer activity of chosen juice cells. After the offer, the activity of chosen juice cells reflected the decision difficulty but did not resemble a race-to-threshold. Finally, chosen value cells presented an "activity overshooting" closely related to the decision difficulty and possibly due to fluctuations in the relative value of the juices. This overshooting was independent of choice hysteresis.

**Contributions of Orbitofrontal and Lateral Prefrontal Cortices to Economic Choice and the Good-to-Action Transformation** Cai X, Padoa-Schioppa C. Neuron. 2014; 81(5): 1140-1151.

Previous work indicates that economic decisions can be made independently of the visuomotor contingencies of the choice task (space of goods). However, the neuronal mechanisms through which the choice outcome (the chosen good) is transformed into a suitable action plan remain poorly understood. Here the authors show that neurons in lateral prefrontal cortex reflect the early stages of this good-to-action transformation. Monkeys chose between different juices. The experimental design dissociated in space and time the presentation of the offers and the saccade targets associated with them. The authors recorded from the orbital, ventrolateral, and dorsolateral prefrontal cortices (OFC, LPFCv, and LPFCd, respectively). Prior to target presentation, neurons in both LPFCv and LPFCd encoded the choice outcome in goods space. After target presentation, they gradually came to encode the location of the targets and the upcoming action plan. Consistent with the anatomical connectivity, all spatial and action-related signals emerged in LPFCv before LPFCd.

**New insights Into The Therapeutic Potential Of Girk Channels** Lujan R, Marron Fernandez de Velasco E, Aguado C, Wickman K. Trends Neurosci 2014; 37(1): 20-29.

G protein-dependent signaling pathways control the activity of excitable cells of the nervous system and heart, and are the targets of neurotransmitters, clinically relevant drugs, and drugs of abuse. G protein-gated inwardly rectifying potassium (K<sup>+</sup>) (Girk/Kir3) channels are a key effector in inhibitory signaling pathways. Girk-dependent signaling contributes to nociception and analgesia, reward-related behavior, mood, cognition, and heart-rate regulation, and has been linked to epilepsy, Down syndrome, addiction, and arrhythmias. The authors discuss recent advances in our understanding of Girk channel structure, organization in signaling complexes, and plasticity, as well as progress on

the development of subunit-selective Girk modulators. These findings offer new hope for the selective manipulation of Girk channels to treat a variety of debilitating afflictions.

#### **Ankyrin-G Directly Binds To Kinesin-1 To Transport Voltage-Gated Na<sup>+</sup> Channels Into Axons**

Barry J, Gu Y, Jukkola P, O'Neill B, Gu H, Mohler PJ, Rajamani KT, Gu C. Dev Cell 2014; 28(2): 117-131.

Action potentials (APs) propagating along axons require the activation of voltage-gated Na<sup>+</sup> (Nav) channels. How Nav channels are transported into axons is unknown. The authors show that KIF5/kinesin-1 directly binds to ankyrin-G (AnkG) to transport Nav channels into axons. KIF5 and Nav1.2 channels bind to multiple sites in the AnkG N-terminal domain that contains 24 ankyrin repeats. Disrupting AnkG-KIF5 binding with small interfering RNA or dominant-negative constructs markedly reduced Nav channel levels at the axon initial segment (AIS) and along entire axons, thereby decreasing AP firing. Live-cell imaging showed that fluorescently tagged AnkG or Nav1.2 cotransported with KIF5 along axons. Deleting AnkG in vivo or virus-mediated expression of a dominant-negative KIF5 construct specifically decreased the axonal level of Nav, but not Kv1.2, channels in mouse cerebellum. These results indicate that AnkG functions as an adaptor to link Nav channels to KIF5 during axonal transport before anchoring them to the AIS and nodes of Ranvier.

#### **Structural Insights Into Assembly and Regulation Of The Plasma Membrane Phosphatidylinositol 4-Kinase Complex**

Wu X, Chi RJ, Baskin JM, Lucast L, Burd CG, De Camilli P, Reinisch KM. Dev Cell 2014; 28(1): 19-29.

Plasma membrane PI4P helps determine the identity of this membrane and plays a key role in signal transduction as the precursor of PI(4,5)P<sub>2</sub> and its metabolites. Here, the authors report the atomic structure of the protein scaffold that is required for the plasma membrane localization and function of Stt4/PI4KIII $\alpha$ , the PI 4-kinase responsible for this PI4P pool. Both proteins of the scaffold, Efr3 and YPP1/TTC7, are composed of  $\alpha$ -helical repeats, which are arranged into a rod in Efr3 and a superhelix in Ypp1. A conserved basic patch in Efr3, which binds acidic phospholipids, anchors the complex to the plasma membrane. Stt4/PI4KIII $\alpha$  is recruited by interacting with the Ypp1 C-terminal lobe, which also binds to unstructured regions in the Efr3 C terminus. Phosphorylation of this Efr3 region counteracts Ypp1 binding, thus providing a mechanism through which Stt4/PI4KIII $\alpha$  recruitment, and thus a metabolic reaction of fundamental importance in cell physiology, can be regulated.

#### **Genome-Wide Association Study Of Alcohol Dependence: Significant Findings In African- and European-Americans Including Novel Risk Loci**

Gelernter J, Kranzler HR, Sherva R, Almasy L, Koesterer R, Smith AH, Anton R, Preuss UW, Ridinger M, Rujescu D, Wodarz N, Zill P, Zhao H, Farrer LA. Mol Psychiatry 2014; 19(1): 41-49.

The authors report a GWAS of alcohol dependence (AD) in European-American (EA) and African-American (AA) populations, with replication in independent samples of EAs, AAs and Germans. Their sample for discovery and replication was 16 087 subjects, the largest sample for AD GWAS to date. Numerous genome-wide significant (GWS) associations were identified, many novel. Most associations were population specific, but in several cases were GWS in EAs and AAs for different SNPs at the same locus, showing biological convergence across populations. The authors confirmed well-known risk loci mapped to alcohol-metabolizing enzyme genes, notably ADH1B (EAs: Arg48His,  $P=1.17 \times 10^{-31}$ ; AAs: Arg369Cys,  $P=6.33 \times 10^{-17}$ ) and ADH1C in AAs (Thr151Thr,  $P=4.94 \times 10^{-10}$ ), and identified novel risk loci mapping to the ADH gene cluster on chromosome 4 and extending centromerically beyond it to include GWS associations at LOC100507053 in AAs ( $P=2.63 \times 10^{-11}$ ), PDLIM5 in EAs ( $P=2.01 \times 10^{-8}$ ), and METAP in AAs ( $P=3.35 \times 10^{-8}$ ). They also identified a novel GWS association ( $1.17 \times 10^{-10}$ ) mapped to chromosome 2 at rs1437396,

between MTIF2 and CCDC88A, across all of the EA and AA cohorts, with supportive gene expression evidence, and population-specific GWS for markers on chromosomes 5, 9 and 19. Several of the novel associations implicate direct involvement of, or interaction with, genes previously identified as schizophrenia risk loci. Confirmation of known AD risk loci supports the overall validity of the study; the novel loci are worthy of genetic and biological follow-up. The findings support a convergence of risk genes (but not necessarily risk alleles) between populations, and, to a lesser extent, between psychiatric traits.

**HIV-1 Chromatin, Transcription, and the Regulatory Protein Tat** Colin L, Verdin E, Van Lint C. Methods Mol Biol 2014; 1087: 85-101.

Upon integration into the host cell genome, the nucleosomal organization and epigenetic control of the HIV-1 provirus play an active role in its transcriptional regulation. Therefore, characterization of the chromatin changes that occur in the viral promoter region in response to different cellular stimuli or drug treatments represents an important aspect of our understanding of HIV-1 transcription. Moreover, the viral transactivator Tat protein potently activates HIV-1 transcription by recruiting the cellular positive transcription elongation factor p-TEFb to the TAR element located at the 5' end of all nascent viral transcripts, thereby promoting efficient elongation. This chapter describes two complementary techniques for analyzing chromatin structure. The first technique is called indirect end-labeling and uses DNase I, micrococcal nuclease (MNase) or specific restriction enzymes to provide a view of nucleosome positions and of nucleosome-free regions within genes that are usually associated with transcriptional regulatory elements. The second technique, called chromatin immunoprecipitation (ChIP), provides a detailed analysis of chromatin structure by determining the pattern of histone modification marks in the DNA region of interest and by identifying the transcription factors as well as the components of the transcriptional initiation and elongation machineries that are recruited in vivo to this chromosomal region.

**Essentials Of Recombinase-Based Genetic Fate Mapping In Mice** Jensen P, Dymecki SM. Methods Mol Biol 2014; 1092: 437-454.

Fate maps, by defining the relationship between embryonic tissue organization and postnatal tissue structure, are one of the most important tools on hand to developmental biologists. In the past, generating such maps in mice was hindered by their in utero development limiting the physical access required for traditional methods involving tracer injection or cell transplantation. No longer is physical access a requirement. Innovations over the past decade have led to genetic techniques that offer means to "deliver" cell lineage tracers noninvasively. Such "genetic fate mapping" approaches employ transgenic strategies to express genetically encoded site-specific recombinases in a cell type-specific manner to switch on expression of a cell-heritable reporter transgene as lineage tracer. The behaviors and fate of marked cells and their progeny can then be explored and their contributions to different tissues examined. Here, the authors review the basic concepts of genetic fate mapping and consider the strengths and limitations for their application. They also explore two refinements of this approach that lend improved spatial and temporal resolution: (1) Intersectional and subtractive genetic fate mapping and (2) Genetic inducible fate mapping.

**Neuronal Ferritin Heavy Chain and Drug Abuse Affect HIV-Associated Cognitive Dysfunction** Pitcher J, Abt A, Myers J, Han R, Snyder M, Graziano A, Festa L, Kutzler M, Garcia F, Gao WJ, Fischer-Smith T, Rappaport J, Meucci O. J Clin Invest 2014; 124(2): 656-669.

Interaction of the chemokine CXCL12 with its receptor CXCR4 promotes neuronal function and survival during embryonic development and throughout adulthood. Previous studies indicated that  $\mu$ -opioid agonists specifically elevate neuronal levels of the protein ferritin heavy chain (FHC), which



negatively regulates CXCR4 signaling and affects the neuroprotective function of the CXCL12/CXCR4 axis. Here, the authors determined that CXCL12/CXCR4 activity increased dendritic spine density, and also examined FHC expression and CXCR4 status in opiate abusers and patients with HIV-associated neurocognitive disorders (HAND), which is typically exacerbated by illicit drug use. Drug abusers and HIV patients with HAND had increased levels of FHC, which correlated with reduced CXCR4 activation, within cortical neurons. The authors confirmed these findings in a nonhuman primate model of SIV infection with morphine administration. Transfection of a CXCR4-expressing human cell line with an iron-deficient FHC mutant confirmed that increased FHC expression deregulated CXCR4 signaling and that this function of FHC was independent of iron binding. Furthermore, examination of morphine-treated rodents and isolated neurons expressing FHC shRNA revealed that FHC contributed to morphine-induced dendritic spine loss. Together, these data implicate FHC-dependent deregulation of CXCL12/CXCR4 as a contributing factor to cognitive dysfunction in neuroAIDS.

**Opioid Receptor-Triggered Spinal Mtorc1 Activation Contributes To Morphine Tolerance and Hyperalgesia** Xu JT, Zhao JY, Zhao X, Ligons D, Tiwari V, Atianjoh FE, Lee CY, Liang L, Zang W, Njoku D, Raja SN, Yaster M, Tao YX. J Clin Invest 2014; 124(2): 592-603.

The development of opioid-induced analgesic tolerance and hyperalgesia is a clinical challenge for managing chronic pain. Adaptive changes in protein translation in the nervous system are thought to promote opioid tolerance and hyperalgesia; however, how opioids drive such changes remains elusive. Here, the authors report that mammalian target of rapamycin (mTOR), which governs most protein translation, was activated in rat spinal dorsal horn neurons after repeated intrathecal morphine injections. Activation was triggered through  $\mu$  opioid receptor and mediated by intracellular PI3K/Akt. Spinal mTOR inhibition blocked both induction and maintenance of morphine tolerance and hyperalgesia, without affecting basal pain perception or locomotor functions. These effects were attributed to the attenuation of morphine-induced increases in translation initiation activity, nascent protein synthesis, and expression of some known key tolerance-associated proteins, including neuronal NOS (nNOS), in dorsal horn. Moreover, elevating spinal mTOR activity by knocking down the mTOR-negative regulator TSC2 reduced morphine analgesia, produced pain hypersensitivity, and increased spinal nNOS expression. These findings implicate the  $\mu$  opioid receptor-triggered PI3K/Akt/mTOR pathway in promoting morphine-induced spinal protein translation changes and associated morphine tolerance and hyperalgesia. These data suggest that mTOR inhibitors could be explored for prevention and/or reduction of opioid tolerance in chronic pain management.

**Repeated  $\delta$ 9-Tetrahydrocannabinol Exposure in Adolescent Monkeys: Persistent Effects Selective for Spatial Working Memory** Verrico CD, Gu H, Peterson ML, Sampson AR, Lewis DA. Am J Psychiatry. 2014 Apr 1; 171(4): 416-425.

Epidemiological findings suggest that, relative to adults, adolescents are more vulnerable to the adverse persistent effects of cannabis on working memory. However, the potential confounds inherent in human studies preclude direct determination of a cause-and-effect relationship between adolescent cannabis use and heightened susceptibility to persistent working memory impairments. Consequently, the authors examined the effects of repeated exposure to  $\Delta$ 9-tetrahydrocannabinol (THC) on performance of spatial and object working memory tasks in adolescent monkeys. Seven pairs of male adolescent rhesus monkeys, matched for baseline cognitive performance, received vehicle or THC intravenously 5 days/week for 6 months. Performance on spatial and object memory tasks was assessed 23 or 71 hours after drug administration throughout the study. In addition, acute effects on working memory were also assessed at the beginning and end of the 6-month period. Relative to the vehicle-exposed control animals, those with repeated THC exposure had a blunted trajectory of

accuracy improvements on the spatial working memory task in a delay-dependent manner. Accuracy improvements on the object working memory task did not differ between groups. Relative to the acute effects of THC on working memory at the beginning of the study, neither sensitivity nor tolerance was evident after 6 months of THC exposure. Because maturation of performance is later for spatial than for object working memory, these findings suggest that persistent effects of THC on cognitive abilities are more evident when exposure coincides with the developmental stage during which the underlying neural circuits are actively maturing.

#### **Integrating GWASs and Human Protein Interaction Networks Identifies A Gene Subnetwork Underlying Alcohol Dependence**

Han S, Yang BZ, Kranzler HR, Liu X, Zhao H, Farrer LA, Boerwinkle E, Potash JB, Gelernter J. Am J Hum Genet 2013; 93(6): 1027-1034.

Despite a significant genetic contribution to alcohol dependence (AD), few AD-risk genes have been identified to date. In the current study, the authors aimed to integrate genome-wide association studies (GWASs) and human protein interaction networks to investigate whether a subnetwork of genes whose protein products interact with one another might collectively contribute to AD. By using two discovery GWAS data sets of the Study of Addiction: Genetics and Environment (SAGE) and the Collaborative Study on the Genetics of Alcoholism (COGA), we identified a subnetwork of 39 genes that not only was enriched for genes associated with AD, but also collectively associated with AD in both European Americans ( $p < 0.0001$ ) and African Americans ( $p = 0.0008$ ). The authors replicated the association of the gene subnetwork with AD in three independent samples, including two samples of European descent ( $p = 0.001$  and  $p = 0.006$ ) and one sample of African descent ( $p = 0.0069$ ). To evaluate whether the significant associations are likely to be false-positive findings and to ascertain their specificity, they examined the same gene subnetwork in three other human complex disorders (bipolar disorder, major depressive disorder, and type 2 diabetes) and found no significant associations. Functional enrichment analysis revealed that the gene subnetwork was enriched for genes involved in cation transport, synaptic transmission, and transmission of nerve impulses, all of which are biologically meaningful processes that may underlie the risk for AD. In conclusion, the authors identified a gene subnetwork underlying AD that is biologically meaningful and highly reproducible, providing important clues for future research into AD etiology and treatment.

#### **Zebrafish As An Emerging Model For Studying Complex Brain Disorders**

Kalueff AV, Stewart AM, Gerlai R. Trends Pharmacol Sci 2014; 35(2): 63-75.

The zebrafish (*Danio rerio*) is rapidly becoming a popular model organism in pharmacogenetics and neuropharmacology. Both larval and adult zebrafish are currently used to increase our understanding of brain function, dysfunction, and their genetic and pharmacological modulation. Here the authors review the developing utility of zebrafish in the analysis of complex brain disorders (including, e.g., depression, autism, psychoses, drug abuse, and cognitive deficits), also covering zebrafish applications towards the goal of modeling major human neuropsychiatric and drug-induced syndromes. The authors argue that zebrafish models of complex brain disorders and drug-induced conditions are a rapidly emerging critical field in translational neuroscience and pharmacology research.

#### **Bath Salts, Mephedrone, and Methylenedioxypyrovalerone As Emerging Illicit Drugs That Will Need Targeted Therapeutic Intervention**

Glennon RA. Adv Pharmacol 2014; 69: 581-620.

The term "synthetic cathinones" is fairly new, but, although the abuse of synthetic cathinones is a recent problem, research on cathinone analogs dates back >100 years. One structural element cathinone analogs have in common is an  $\alpha$ -aminophenone moiety. Introduction of amine and/or aryl substituents affords a large number of agents. Today, >40 synthetic cathinones have been identified on the clandestine market and many have multiple "street names." Many cathinone analogs, although not

referred to as such until the late 1970s, were initially prepared as intermediates in the synthesis of ephedrine analogs. The cathinones do not represent a pharmacologically or mechanistically homogeneous class of agents. Currently abused synthetic cathinones are derived from earlier agents and seem to produce their actions primarily via the dopamine, norepinephrine, and/or serotonin transporter; that is, they either release and/or inhibit the reuptake of one or more of these neurotransmitters. The actions of these agents can resemble those of central stimulants such as methamphetamine, cocaine, and/or empathogens such as 1-(3,4-methylenedioxyphe-nyl)-2-aminopropane (Ecstasy) and/or produce other effects. Side effects are primarily of a neurological and/or cardiovascular nature. The use of the "and/or" term is emphasized because synthetic cathinones represent a broad class of agents that produce a variety of actions; the agents cannot be viewed as being pharmacologically equivalent. Until valid structure-activity relationships are formulated for each behavioral/mechanistic action, individual synthetic cathinones remain to be evaluated on a case-by-case basis. Treatment of synthetic cathinone intoxication requires more "basic science" research. At this time, treatment is mostly palliative.

**New Directions In Nicotine Vaccine Design and Use** Pentel PR, LeSage MG. Adv Pharmacol 2014; 69: 553-580.

Clinical trials of nicotine vaccines suggest that they can enhance smoking cessation rates but do not reliably produce the consistently high serum antibody concentrations required. A wide array of next-generation strategies are being evaluated to enhance vaccine efficacy or provide antibody through other mechanisms. Protein conjugate vaccines may be improved by modifications of hapten or linker design or by optimizing hapten density. Conjugating hapten to viruslike particles or disrupted virus may allow exploitation of naturally occurring viral features associated with high immunogenicity. Conjugates that utilize different linker positions on nicotine can function as independent immunogens, so that using them in combination generates higher antibody concentrations than can be produced by a single immunogen. Nanoparticle vaccines, consisting of hapten, T cell help peptides, and adjuvants attached to a liposome or synthetic scaffold, are in the early stages of development. Nanoparticle vaccines offer the possibility of obtaining precise and consistent control of vaccine component stoichiometry and spacing and immunogen size and shape. Passive transfer of nicotine-specific monoclonal antibodies offers a greater control of antibody dose, the ability to give very high doses, and an immediate onset of action but is expensive and has a shorter duration of action than vaccines. Viral vector-mediated transfer of genes for antibody production can elicit high levels of antibody expression in animals and may present an alternative to vaccination or passive immunization if the long-term safety of this approach is confirmed. Next-generation immunotherapies are likely to be substantially more effective than first-generation vaccines.

**Bupropion and Bupropion Analogs As Treatments For CNS Disorders** Carroll FI, Blough BE, Mascarella SW, Navarro HA, Lukas RJ, Damaj MI. Adv Pharmacol 2014; 69: 177-216.

Bupropion, introduced as an antidepressant in the 1980s, is also effective as a smoking cessation aid and is beneficial in the treatment of methamphetamine addiction, cocaine dependence, addictive behaviors such as pathological gambling, and attention deficit hyperactivity disorder. (2S,3S)-hydroxybupropion is an active metabolite of bupropion produced in humans that contributes to antidepressant and smoking cessation efficacy and perhaps benefits in other CNS disorders. Mechanisms underlying its antidepressant and smoking abstinence remain elusive. However, it seems likely that efficacy is due to a combination of the effects of bupropion and/or its active metabolite (2S,3S)-hydroxybupropion involving the inhibition of reuptake of dopamine (DA) and NE in reward centers of the brain and the noncompetitive antagonism of  $\alpha 4\beta 2$ - and  $\alpha 3\beta 4^*$ -nAChRs. These combined effects of bupropion and its active metabolite may be responsible for its ability to decrease nicotine

reward and withdrawal. Studies directed toward development of a bupropion analog for treatment of cocaine addiction led to compounds, typified by 2-(N-cyclopropylamino)-3'-chloropropiophenone (RTI-6037-39), thought to act as indirect DA agonists. In addition, (2S,3S)-hydroxybupropion analogs were developed, which had varying degrees of DA and NE uptake inhibition and antagonism of nAChRs. These compounds will be valuable tools for animal behavioral studies and as clinical candidates. Here, the authors review the (1) early studies leading to the development of bupropion, (2) bupropion metabolism and the identification of (2S,3R)-hydroxybupropion as an active metabolite, (3) mechanisms of bupropion and metabolite action, (4) effects in animal behavioral studies, (5) results of clinical studies, and (6) development of bupropion analogs as potential pharmacotherapies for treating nicotine and cocaine addiction.

**A Fully Genetically Encoded Protein Architecture For Optical Control Of Peptide Ligand Concentration** Schmidt D, Tillberg PW, Chen F, Boyden ES. Nat Commun 2014; 5: 3019.

Ion channels are among the most important proteins in biology, regulating the activity of excitable cells and changing in diseases. Ideally it would be possible to actuate endogenous ion channels, in a temporally precise and reversible manner, and without requiring chemical cofactors. Here the authors present a modular protein architecture for fully genetically encoded, light-modulated control of ligands that modulate ion channels of a targeted cell. Their reagent, which we call a lumitoxin, combines a photoswitch and an ion channel-blocking peptide toxin. Illumination causes the photoswitch to unfold, lowering the toxin's local concentration near the cell surface, and enabling the ion channel to function. The authors explore lumitoxin modularity by showing operation with peptide toxins that target different voltage-dependent K(+) channels. The lumitoxin architecture may represent a new kind of modular protein-engineering strategy for designing light-activated proteins, and thus may enable development of novel tools for modulating cellular physiology.

**Total Syntheses of (-)-Pyrimidoblamic Acid and P-3A** Duerfeldt AS, Boger DL. J Am Chem Soc 2014; 136(5): 2119-2125.

Total syntheses of (-)-pyrimidoblamic acid and P-3A are disclosed. Central to the convergent approach is a powerful inverse electron demand Diels-Alder reaction between substituted electron-deficient 1,2,3-triazines and a highly functionalized and chiral primary amidine, which forms the pyrimidine cores and introduces all necessary stereochemistry in a single step. Intrinsic in the convergent approach is the potential it provides for the late stage divergent synthesis of modified analogs bearing deep-seated changes in either the pyrimidine cores or the highly functionalized C2 side chain common to both natural products. The examination of the key cycloaddition reaction revealed that the inherent 1,2,3-triazine mode of cycloaddition (C4/N1 vs C5/N2) as well as the amidine regioselectivity were unaffected by introduction of two electron-withdrawing groups (-CO<sub>2</sub>R) at C4 and C6 of the 1,2,3-triazine even if C5 is unsubstituted (Me or H), highlighting the synthetic potential of the powerful pyrimidine synthesis.

**Remodeling Natural Products: Chemistry and Serine Hydrolase Activity of a Rocaglate-Derived  $\beta$ -Lactone** Lajkiewicz NJ, Cognetta 3rd AB, Niphakis MJ, Cravatt BF, Porco Jr JA. J Am Chem Soc 2014; 136(6): 2659-2664.

Flavaglines are a class of natural products with potent insecticidal and anticancer activities.  $\beta$ -Lactones are a privileged structural motif found in both therapeutic agents and chemical probes. Herein, the authors report the synthesis, unexpected light-driven di-epimerization, and activity-based protein profiling of a novel rocaglate-derived  $\beta$ -lactone. In addition to in vitro inhibition of the serine hydrolases ABHD10 and ACOT1/2, the most potent  $\beta$ -lactone enantiomer was also found to inhibit these enzymes, as well as the serine peptidases CTSA and SCPEP1, in PC3 cells.

**Essential Role Of Poly(ADP-Ribosyl)ation In Cocaine Action** Scobie KN, Damez-Werno D, Sun H, Shao N, Gancarz A, Panganiban CH, Dias C, Koo J, Caiafa P, Kaufman L, Neve RL, Dietz DM, Shen L, Nestler EJ. Proc Natl Acad Sci U S A 2014; 111(5): 2005-1010.

Many of the long-term effects of cocaine on the brain's reward circuitry have been shown to be mediated by alterations in gene expression. Several chromatin modifications, including histone acetylation and methylation, have been implicated in this regulation, but the effect of other histone modifications remains poorly understood. Poly(ADP-ribose) polymerase-1 (PARP-1), a ubiquitous and abundant nuclear protein, catalyzes the synthesis of a negatively charged polymer called poly(ADP-ribose) or PAR on histones and other substrate proteins and forms transcriptional regulatory complexes with several other chromatin proteins. Here, the authors identify an essential role for PARP-1 in cocaine-induced molecular, neural, and behavioral plasticity. Repeated cocaine administration, including self-administration, increased global levels of PARP-1 and its mark PAR in mouse nucleus accumbens (NAc), a key brain reward region. Using PARP-1 inhibitors and viral-mediated gene transfer, they established that PARP-1 induction in NAc mediates enhanced behavioral responses to cocaine, including increased self-administration of the drug. Using chromatin immunoprecipitation sequencing, they demonstrated a global, genome-wide enrichment of PARP-1 in NAc of cocaine-exposed mice and identified several PARP-1 target genes that could contribute to the lasting effects of cocaine. Specifically, they identified sidekick-1--important for synaptic connections during development--as a critical PARP-1 target gene involved in cocaine's behavioral effects as well as in its ability to induce dendritic spines on NAc neurons. These findings establish the involvement of PARP-1 and PARylation in the long-term actions of cocaine.

**The Long Noncoding RNA THRIL Regulates TNF\* Expression Through Its Interaction With hnRNPL** Li Z, Chao TC, Chang KY, Lin N, Patil VS, Shimizu C, Head SR, Burns JC, Rana TM. Proc Natl Acad Sci U S A 2014; 111(3): 1002-1007.

Thousands of large intergenic noncoding RNAs (lincRNAs) have been identified in the mammalian genome, many of which have important roles in regulating a variety of biological processes. Here, the authors used a custom microarray to identify lincRNAs associated with activation of the innate immune response. A panel of 159 lincRNAs was found to be differentially expressed following innate activation of THP1 macrophages. Among them, linc1992 was shown to be expressed in many human tissues and was required for induction of TNF $\alpha$  expression. Linc1992 bound specifically to heterogenous nuclear ribonucleoprotein L (hnRNPL) and formed a functional linc1992-hnRNPL complex that regulated transcription of the TNF $\alpha$  gene by binding to its promoter. Transcriptome analysis revealed that linc1992 was required for expression of many immune-response genes, including other cytokines and transcriptional and posttranscriptional regulators of TNF $\alpha$  expression, and that knockdown of linc1992 caused dysregulation of these genes during innate activation of THP1 macrophages. Therefore, the authors named linc1992 THRIL (TNF $\alpha$  and hnRNPL related immunoregulatory LincRNA). Finally, THRIL expression was correlated with the severity of symptoms in patients with Kawasaki disease, an acute inflammatory disease of childhood. Collectively, these data provide evidence that lincRNAs and their binding proteins can regulate TNF $\alpha$  expression and may play important roles in the innate immune response and inflammatory diseases in humans.

**Activation Of Gabaergic Neurons In the Interpeduncular Nucleus Triggers Physical Nicotine Withdrawal Symptoms** Zhao-Shea R, Liu L, Pang X, Gardner PD, Tapper AR. Curr Biol 2013; 23(23): 2327-2335.

Chronic exposure to nicotine elicits physical dependence in smokers, yet the mechanism and neuroanatomical bases for withdrawal symptoms are unclear. As in humans, rodents undergo physical withdrawal symptoms after cessation from chronic nicotine characterized by increased scratching, head nods, and body shakes. Here the authors show that induction of physical nicotine withdrawal symptoms activates GABAergic neurons within the interpeduncular nucleus (IPN). Optical activation of IPN GABAergic neurons via light stimulation of channelrhodopsin elicited physical withdrawal symptoms in both nicotine-naïve and chronic-nicotine-exposed mice. Dampening excitability of GABAergic neurons during nicotine withdrawal through IPN-selective infusion of an NMDA receptor antagonist or through blockade of IPN neurotransmission from the medial habenula reduced IPN neuronal activation and alleviated withdrawal symptoms. During chronic nicotine exposure, nicotinic acetylcholine receptors containing the  $\beta 4$  subunit were upregulated in somatostatin interneurons clustered in the dorsal region of the IPN. Blockade of these receptors induced withdrawal signs more dramatically in nicotine-dependent compared to nicotine-naïve mice and activated nonsomatostatin neurons in the IPN. Together, these data indicate that therapeutic strategies to reduce IPN GABAergic neuron excitability during nicotine withdrawal, for example, by activating nicotinic receptors on somatostatin interneurons, may be beneficial for alleviating withdrawal symptoms and facilitating smoking cessation.

**A Novel Analgesic Isolated From A Traditional Chinese Medicine** Zhang Y, Wang C, Wang L, Parks GS, Zhang X, Guo Z, Ke Y, Li KW, Kim MK, Vo B, Borrelli E, Ge G, Yang L, Wang Z, Garcia-Fuster MJ, Luo ZD, Liang X, Civelli O. Curr Biol 2014; 24(2): 117-123.

Current pain management is limited, in particular, with regard to chronic pain. In an attempt to discover novel analgesics, the authors combined the approach developed to characterize traditional Chinese medicine (TCM), as part of the "herbalome" project, with the reverse pharmacology approach aimed at discovering new endogenous transmitters and hormones. In a plant used for centuries for its analgesic properties, the authors identify a compound, dehydrocorybulbine (DHCB), that is effective at alleviating thermally induced acute pain. They synthesize DHCB and show that it displays moderate dopamine receptor antagonist activities. By using selective pharmacological compounds and dopamine receptor knockout (KO) mice, they show that DHCB antinociceptive effect is primarily due to its interaction with D2 receptors, at least at low doses. They further show that DHCB is effective against inflammatory pain and injury-induced neuropathic pain and furthermore causes no antinociceptive tolerance. This study casts DHCB as a different type of analgesic compound and as a promising lead in pain management.

**Tools For Resolving Functional Activity and Connectivity Within Intact Neural Circuits** Jennings JH, Stuber GD. Curr Biol 2014; 24(1): R41-50.

Mammalian neural circuits are sophisticated biological systems that choreograph behavioral processes vital for survival. While the inherent complexity of discrete neural circuits has proven difficult to decipher, many parallel methodological developments promise to help delineate the function and connectivity of molecularly defined neural circuits. Here, the authors review recent technological advances designed to precisely monitor and manipulate neural circuit activity. They propose a holistic, multifaceted approach for unraveling how behavioral states are manifested through the cooperative interactions between discrete neurocircuit elements.

**An In-Depth Comparison Of Latent HIV-1 Reactivation In Multiple Cell Model Systems and Resting CD4+ T Cells From Aviremic Patients**

Spina CA, Anderson J, Archin NM, Bosque A, Chan J, Famiglietti M, Greene WC, Kashuba A, Lewin SR, Margolis DM, Mau M, Ruelas D, Saleh S, Shirakawa K, Siliciano RF, Singhania A, Soto PC, Terry VH, Verdin E, Woelk C, Wooden S, Xing S, Planelles V. PLoS Pathog 2013; 9(12): e1003834.

The possibility of HIV-1 eradication has been limited by the existence of latently infected cellular reservoirs. Studies to examine control of HIV latency and potential reactivation have been hindered by the small numbers of latently infected cells found in vivo. Major conceptual leaps have been facilitated by the use of latently infected T cell lines and primary cells. However, notable differences exist among cell model systems. Furthermore, screening efforts in specific cell models have identified drug candidates for "anti-latency" therapy, which often fail to reactivate HIV uniformly across different models. Therefore, the activity of a given drug candidate, demonstrated in a particular cellular model, cannot reliably predict its activity in other cell model systems or in infected patient cells, tested ex vivo. This situation represents a critical knowledge gap that adversely affects our ability to identify promising treatment compounds and hinders the advancement of drug testing into relevant animal models and clinical trials. To begin to understand the biological characteristics that are inherent to each HIV-1 latency model, the authors compared the response properties of five primary T cell models, four J-Lat cell models and those obtained with a viral outgrowth assay using patient-derived infected cells. A panel of thirteen stimuli that are known to reactivate HIV by defined mechanisms of action was selected and tested in parallel in all models. These results indicate that no single in vitro cell model alone is able to capture accurately the ex vivo response characteristics of latently infected T cells from patients. Most cell models demonstrated that sensitivity to HIV reactivation was skewed toward or against specific drug classes. Protein kinase C agonists and PHA reactivated latent HIV uniformly across models, although drugs in most other classes did not.

**Behavior Of Knock-In Mice With A Cocaine-Insensitive Dopamine Transporter After Virogenetic Restoration Of Cocaine Sensitivity In the Striatum**

O'Neill B, Tilley MR, Han DD, Thirtamara-Rajamani K, Hill ER, Bishop GA, Zhou FM, During MJ, Gu HH. Neuropharmacology 2014; 79: 626-633.

Cocaine's main pharmacological actions are the inhibition of the dopamine, serotonin, and norepinephrine transporters. Its main behavioral effects are reward and locomotor stimulation, potentially leading to addiction. Using knock-in mice with a cocaine-insensitive dopamine transporter (DAT-CI mice) the authors have shown previously that inhibition of the dopamine transporter (DAT) is necessary for both of these behaviors. In this study, they sought to determine brain regions in which DAT inhibition by cocaine stimulates locomotor activity and/or produces reward. They used adeno-associated viral vectors to re-introduce the cocaine-sensitive wild-type DAT in specific brain regions of DAT-CI mice, which otherwise only express a cocaine-insensitive DAT globally. Viral-mediated expression of wild-type DAT in the rostralateral striatum restored cocaine-induced locomotor stimulation and sensitization in DAT-CI mice. In contrast, the expression of wild-type DAT in the dorsal striatum, or in the medial nucleus accumbens, did not restore cocaine-induced locomotor stimulation. These data help to determine cocaine's molecular actions and anatomical loci that cause hyperlocomotion. Interestingly, cocaine did not produce significant reward - as measured by conditioned place-preference - in any of the three cohorts of DAT-CI mice with the virus injections. Therefore, the locus or loci underlying cocaine-induced reward remain underdetermined. It is possible that multiple dopamine-related brain regions are involved in producing the robust rewarding effect of cocaine.

### **Genetic Variation Within the Chrna7 Gene Modulates Nicotine Reward-Like Phenotypes In**

**Mice** Harenza JL, Muldoon PP, De Biasi M, Damaj MI, Miles MF. *Genes Brain Behav* 2014; 13(2): 213-225.

Mortality from tobacco smoking remains the leading cause of preventable death in the world, yet current cessation therapies are only modestly successful, suggesting new molecular targets are needed. Genetic analysis of gene expression and behavior identified Chrna7 as potentially modulating nicotine place conditioning in the BXD panel of inbred mice. The authors used gene targeting and pharmacological tools to confirm the role of Chrna7 in nicotine conditioned place preference (CPP). To identify molecular events downstream of Chrna7 that may modulate nicotine preference, they performed microarray analysis of  $\alpha 7$  knock-out (KO) and wild-type (WT) nucleus accumbens (NAc) tissue, followed by confirmation with quantitative polymerase chain reaction (PCR) and immunoblotting. In the BXD panel, they found a putative cis expression quantitative trait loci (eQTL) for Chrna7 in NAc that correlated inversely to nicotine CPP. They observed that gain-of-function  $\alpha 7$  mice did not display nicotine preference at any dose tested, whereas conversely,  $\alpha 7$  KO mice demonstrated nicotine place preference at a dose below that routinely required to produce preference. In B6 mice, the  $\alpha 7$  nicotinic acetylcholine receptor (nAChR)-selective agonist, PHA-543613, dose-dependently blocked nicotine CPP, which was restored using the  $\alpha 7$  nAChR-selective antagonist, methyllycaconitine citrate (MLA). These genomic studies implicated a messenger RNA (mRNA) co-expression network regulated by Chrna7 in NAc. Mice lacking Chrna7 demonstrate increased insulin signaling in the NAc, which may modulate nicotine place preference. These studies provide novel targets for future work on development of more effective therapeutic approaches to counteract the rewarding properties of nicotine for smoking cessation.

### **Blockade Of Hypocretin Receptor-1 Preferentially Prevents Cocaine Seeking: Comparison With Natural Reward Seeking**

Martin-Fardon R, Weiss F. *Neuroreport* 2014.

Hypothalamic orexin/hypocretin (Orx/Hcrt) peptides participate in the regulation of a wide range of physiological processes and are recruited by drugs of abuse. To advance our understanding of the potential of the Orx/Hcrt receptor-1 (Hcrt-r1) as a treatment target for cocaine addiction, the effect of SB334867 [N-(2-methyl-6-benzoxazolyl)-N'-1,5-naphthyridin-4-yl urea], a specific Hcrt-r1 antagonist, on reinstatement elicited by cocaine-associated stimuli versus stimuli associated with a highly palatable conventional reinforcer [sweetened condensed milk (SCM)] was tested. Two separate groups of male Wistar rats were trained to associate a discriminative stimulus (S) with the response-contingent availability of cocaine (0.25 mg/0.1 ml/infusion) or SCM [2/1 (v/v)] and subjected to reinstatement tests following extinction of cocaine-reinforced or SCM-reinforced behavior, during which the reinforcers and S were withheld. Following extinction, presentation of the cocaine or SCM S produced comparable recovery of responding. Hcrt-r1 blockade by SB334867 (1-10 mg/kg, intraperitoneal) dose-dependently and selectively reversed conditioned reinstatement induced by cocaine-related stimuli, without interfering with reward seeking produced by the same stimulus when conditioned to SCM. The findings suggest an important role for Hcrt-r1 in appetitive behavior controlled by reward-related stimuli with selectivity for cocaine seeking and identify Hcrt-r1 as a potential treatment target for cocaine relapse prevention.

### **Therapy For Latent HIV-1 Infection: The Role Of Histone Deacetylase Inhibitors**

Manson McManamy ME, Hakre S, Verdin EM, Margolis DM. *Antivir Chem Chemother* 2014; 23(4): 145-149. Persistence of HIV-1 in latently infected CD4(+) T-cells prevents eradication in HIV-infected treated patients. Latency is characterized by a reversible silencing of transcription of integrated HIV-1. Several molecular mechanisms have been described which contribute to latency, including the establishment and maintenance of repressive chromatin on the HIV-1 promoter. Histone deacetylation is a landmark



modification associated with transcriptional repression of the HIV-1 promoter and inhibition of histone deacetylase enzymes (HDACs) reactivates latent HIV-1. Here, we review the different HDAC inhibitors that have been studied in HIV-1 latency and their therapeutic potential in reactivating latent HIV-1.

**Group III Metabotropic Glutamate Receptors and Drug Addiction** Mao L, Guo M, Jin D, Xue B, Wang JQ. Front Med 2013; 7(4): 445-451.

Neuroadaptations of glutamatergic transmission in the limbic reward circuitry are linked to persistent drug addiction. Accumulating data have demonstrated roles of ionotropic glutamate receptors and group I and II metabotropic glutamate receptors (mGluRs) in this event. Emerging evidence also identifies G $\alpha$ i/o-coupled group III mGluRs (mGluR4/7/8 subtypes enriched in the limbic system) as direct substrates of drugs of abuse and active regulators of drug action. Auto- and heteroreceptors of mGluR4/7/8 reside predominantly on nerve terminals of glutamatergic corticostriatal and GABAergic striatopallidal pathways, respectively. These presynaptic receptors regulate basal and/or phasic release of respective transmitters to maintain basal ganglia homeostasis. In response to operant administration of common addictive drugs, such as psychostimulants (cocaine and amphetamine), alcohol and opiates, limbic group III mGluRs undergo drastic adaptations to contribute to the enduring remodeling of excitatory synapses and to usually suppress drug seeking behavior. As a result, a loss-of-function mutation (knockout) of individual group III receptor subtypes often promotes drug seeking. This review summarizes the data from recent studies on three group III receptor subtypes (mGluR4/7/8) expressed in the basal ganglia and analyzes their roles in the regulation of dopamine and glutamate signaling in the striatum and their participation in the addictive properties of three major classes of drugs (psychostimulants, alcohol, and opiates).

**White Matter Connectivity and Aerobic Fitness In Male Adolescents** Herting MM, Colby JB, Sowell ER, Nagel BJ. Dev Cogn Neurosci 2014; 7: 65-75.

Exercise has been shown to have positive effects on the brain and behavior throughout various stages of the lifespan. However, little is known about the impact of exercise on neurodevelopment during the adolescent years, particularly with regard to white matter microstructure, as assessed by diffusion tensor imaging (DTI). Both tract-based spatial statistics (TBSS) and tractography-based along-tract statistics were utilized to examine the relationship between white matter microstructure and aerobic exercise in adolescent males, ages 15-18. Furthermore, the authors examined the data by both (1) grouping individuals based on aerobic fitness self-reports (high fit (HF) vs. low fit (LF)), and (2) using VO<sub>2</sub> peak as a continuous variable across the entire sample. Results showed that HF youth had an overall higher number of streamline counts compared to LF peers, which was driven by group differences in corticospinal tract (CST) and anterior corpus callosum (Fminor). In addition, VO<sub>2</sub> peak was negatively related to FA in the left CST. Together, these results suggest that aerobic fitness relates to white matter connectivity and microstructure in tracts carrying frontal and motor fibers during adolescence. Furthermore, the current study highlights the importance of considering the environmental factor of aerobic exercise when examining adolescent brain development.

**Adolescents Let Sufficient Evidence Accumulate Before Making A Decision When Large Incentives Are At Stake** Teslovich T, Mulder M, Franklin NT, Ruberry EJ, Millner A, Somerville LH, Simen P, Durston S, Casey BJ. Dev Sci 2014; 17(1): 59-70.

Adolescent decision-making has been described as impulsive and suboptimal in the presence of incentives. In this study the authors examined the neural substrates of adolescent decision-making using a perceptual discrimination task for which small and large rewards were associated with correctly detecting the direction of motion of a cloud of moving dots. Adults showed a reward bias of

faster reaction times on trials for which the direction of motion was associated with a large reward. Adolescents, in contrast, were slower to make decisions on trials associated with large rewards. This behavioral pattern in adolescents was paralleled by greater recruitment of fronto-parietal regions important in representing the accumulation of evidence sufficient for selecting one choice over its alternative and the certainty of that choice. The findings suggest that when large incentives are dependent on performance, adolescents may require more evidence to accumulate prior to responding, to be certain to maximize their gains. Adults, in contrast, appear to be quicker in evaluating the evidence for a decision when primed by rewards. Overall these findings suggest that rather than reacting hastily, adolescents can be incentivized to take more time to make decisions when large rewards are at stake.

**Crystallographic Study of FABP5 As An Intracellular Endocannabinoid Transporter** Sanson B, Wang T, Sun J, Wang L, Kaczocha M, Ojima I, Deutsch D, Li H. *Acta Crystallogr D Biol Crystallogr*. 2014 Feb; 70(Pt 2): 290-298.

In addition to binding intracellular fatty acids, fatty-acid-binding proteins (FABPs) have recently been reported to also transport the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG), arachidonic acid derivatives that function as neurotransmitters and mediate a diverse set of physiological and psychological processes. To understand how the endocannabinoids bind to FABPs, the crystal structures of FABP5 in complex with AEA, 2-AG and the inhibitor BMS-309403 were determined. These ligands are shown to interact primarily with the substrate-binding pocket via hydrophobic interactions as well as a common hydrogen bond to the Tyr131 residue. This work advances our understanding of FABP5-endocannabinoid interactions and may be useful for future efforts in the development of small-molecule inhibitors to raise endocannabinoid levels.

**[Dmt1]DALDA Analogues With Enhanced  $\mu$  Opioid Agonist Potency and With A Mixed  $\mu/\kappa$  Opioid Activity Profile** Bai L, Li Z, Chen J, Chung NN, Wilkes BC, Li T, Schiller PW. *Bioorg Med Chem*. 2014 Feb 19. [epub ahead of print].

Analogues of [Dmt1]DALDA (H-Dmt-d-Arg-Phe-Lys-NH<sub>2</sub>; Dmt=2',6'-dimethyltyrosine), a potent  $\mu$  opioid agonist peptide with mitochondria-targeted antioxidant activity, were prepared by replacing Phe3 with various 2',6'-dialkylated Phe analogues, including 2',6'-dimethylphenylalanine (Dmp), 2',4',6'-trimethylphenylalanine (Tmp), 2'-isopropyl-6'-methylphenylalanine (Imp) and 2'-ethyl-6'-methylphenylalanine (Emp), or with the bulky amino acids 3'-(1-naphthyl)alanine (1-Nal), 3'-(2-naphthyl)alanine (2-Nal) or Trp. Several compounds showed significantly increased  $\mu$  agonist potency, retained  $\mu$  receptor selectivity and are of interest as drug candidates for neuropathic pain treatment. Surprisingly, the Dmp3-, Imp3-, Emp3- and 1-Nal3-containing analogues showed much increased  $\kappa$  receptor binding affinity and had mixed  $\mu/\kappa$  properties. In these cases, molecular dynamics studies indicated conformational preorganization of the unbound peptide ligands due to rotational restriction around the C $\beta$ C $\gamma$  bond of the Xxx3 residue, in correlation with the observed  $\kappa$  receptor binding enhancement. Compounds with a mixed  $\mu/\kappa$  opioid activity profile are known to have therapeutic potential for treatment of cocaine abuse.

**A Novel A4/7-Conotoxin Lvia From Conus Lividus That Selectively Blocks A3 $\beta$ 2 Vs. A6/A3 $\beta$ 2 $\beta$ 3 Nicotinic Acetylcholine Receptors** Luo S, Zhangsun D, Schroeder CI, Zhu X, Hu Y, Wu Y, Weltzin MM, Eberhard S, Kaas Q, Craik DJ, McIntosh JM, Whiteaker P. *FASEB J*. 2014 Jan 7. [Epub ahead of print].

This study was performed to discover and characterize the first potent  $\alpha$ 3 $\beta$ 2-subtype-selective nicotinic acetylcholine receptor (nAChR) ligand. A novel  $\alpha$ 4/7-conotoxin,  $\alpha$ -CTxLvIA, was cloned from *Conus lividus*. Its pharmacological profile at *Xenopus laevis* oocyte-expressed rat nAChR subtypes was

determined by 2-electrode voltage-clamp electrophysiology, and its 3-dimensional (3D) structure was determined by NMR spectroscopy.  $\alpha$ -CTx LvIA is a 16-aa C-terminally-amidated peptide with 2-disulfide bridges. Using rat subunits expressed in *Xenopus* oocytes, the authors found the highest affinity of  $\alpha$ -CTxLvIA was for  $\alpha 3\beta 2$  nAChRs (IC<sub>50</sub> 8.7 nM), where blockade was reversible within 2 min. IC<sub>50</sub> values were >100 nM at  $\alpha 6/\alpha 3\beta 2\beta 3$ ,  $\alpha 6/\alpha 3\beta 4$ , and  $\alpha 3\beta 4$  nAChRs, and  $\geq 3$   $\mu$ M at all other subtypes tested.  $\alpha 3\beta 2$  vs.  $\alpha 6\beta 2$  subtype selectivity was confirmed for human-subunit nAChRs with much greater preference (300-fold) for  $\alpha 3\beta 2$  over  $\alpha 6\beta 2$  nAChRs. This is the first  $\alpha$ -CTx reported to show high selectivity for human  $\alpha 3\beta 2$  vs.  $\alpha 6\beta 2$  nAChRs.  $\alpha$ -CTxLvIA adopts two similarly populated conformations water: one (assumed to be bioactive) is highly structured, whereas the other is mostly random coil in nature. Selectivity differences with the similarly potent, but less selective,  $\alpha 3\beta 2$  nAChR antagonist  $\alpha$ -CTx PeIA probably reside within the three residues, which differ in loop 2, given their otherwise similar 3D structures.

### **Loss of Morphine Reward and Dependence in Mice Lacking G Protein-Coupled Receptor Kinase**

**5** Glück L, Loktev A, Moulédous L, Mollereau C, Law PY, Schulz S. Biol Psychiatry. 2014 Feb 3 [Epub ahead of print].

The clinical benefits of opioid drugs are counteracted by the development of tolerance and addiction. The authors provide in vivo evidence for the involvement of G protein-coupled receptor kinases (GRKs) in opioid dependence in addition to their roles in agonist-selective mu-opioid receptor (MOR) phosphorylation. In vivo MOR phosphorylation was examined by immunoprecipitation and nanoflow liquid chromatography-tandem mass spectrometry analysis. Using the hot-plate and conditioned place preference test, we investigated opioid-related antinociception and reward effects in mice lacking GRK3 or GRK5. Etonitazene and fentanyl stimulated the in vivo phosphorylation of multiple carboxyl-terminal phosphate acceptor sites, including threonine 370, serine 375, and threonine 379, which was predominantly mediated by GRK3. By contrast, morphine promoted a selective phosphorylation of serine 375 that was predominantly mediated by GRK5. In contrast to GRK3 knockout mice, GRK5 knockout mice exhibited reduced antinociceptive responses after morphine administration and developed morphine tolerance similar to wild-type mice but fewer signs of physical dependence. Also, morphine was ineffective in inducing conditioned place preference in GRK5 knockout mice, whereas cocaine conditioned place preference was retained. However, the reward properties of morphine were evident in knock-in mice expressing a phosphorylation-deficient S375A mutation of the MOR. These findings show for the first time that MOR phosphorylation is regulated by agonist-selective recruitment of distinct GRK isoforms that influence different opioid-related behaviors. Modulation of GRK5 function could serve as a new approach for preventing addiction to opioids, while maintaining the analgesic properties of opioid drugs at an effective level.

### **Pharmacology Of Novel Synthetic Stimulants Structurally Related To the "Bath Salts"**

**Constituent 3,4-Methylenedioxypyrovalerone (MDPV)** Marusich JA, Antonazzo KR, Wiley JL, Blough BE, Partilla JS, Baumann MH. Neuropharmacology. 2014 Mar 2. pii: S0028-3908(14)00080-X. [Epub ahead of print].

There has been a dramatic rise in the abuse of synthetic cathinones known as "bath salts," including 3,4-methylenedioxypyrovalerone (MDPV), an analog linked to many adverse events. MDPV differs from other synthetic cathinones because it contains a pyrrolidine ring which gives the drug potent actions as an uptake blocker at dopamine and norepinephrine transporters. While MDPV is now illegal, a wave of "second generation" pyrrolidinophenones has appeared on the market, with  $\alpha$ -pyrrolidinovalerophenone ( $\alpha$ -PVP) being most popular. Here, the authors sought to compare the in vitro and in vivo pharmacological effects of MDPV and its congeners:  $\alpha$ -PVP,  $\alpha$ -pyrrolidinobutiophenone ( $\alpha$ -PBP), and  $\alpha$ -pyrrolidinopropiophenone ( $\alpha$ -PPP). They examined effects of

test drugs in transporter uptake and release assays using rat brain synaptosomes, then assessed behavioral stimulant effects in mice. They found that  $\alpha$ -PVP is a potent uptake blocker at dopamine and norepinephrine transporters, similar to MDPV.  $\alpha$ -PBP and  $\alpha$ -PPP are also catecholamine transporter blockers but display reduced potency. All of the test drugs are locomotor stimulants, and the rank order of in vivo potency parallels dopamine transporter activity, with MDPV >  $\alpha$ -PVP >  $\alpha$ -PBP >  $\alpha$ -PPP. Motor activation produced by all drugs is reversed by the dopamine receptor antagonist SCH23390. Furthermore, results of a functional observational battery show that all test drugs produce typical stimulant effects at lower doses and some drugs produce bizarre behaviors at higher doses. Taken together, these findings represent the first evidence that second generation analogs of MDPV are catecholamine-selective uptake blockers which may pose risk for addiction and adverse effects in human users. This article is part of a Special Issue entitled 'CNS Stimulants'.

## **BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH**

### **The Superior Longitudinal Fasciculus in Typically Developing Children and Adolescents**

**Diffusion Tensor Imaging and Neuropsychological Correlates** Urger S, De Bellis M, Hooper S, Woolley D, Chen S, Provenzale J. J Child Neurol. 2014 Feb 19.

The relationship between superior longitudinal fasciculus microstructural integrity and neuropsychological functions were examined in 49 healthy children (range: 5-17 years) using diffusion tensor imaging. Seven major cognitive domains (intelligence, fine-motor, attention, language, visual-spatial, memory, executive function) were assessed. Data analyses used correlational methods. After adjusting for age and gender, fractional anisotropy and axial diffusivity values in the superior longitudinal fasciculus were positively correlated with executive functions of set shifting, whereas left superior longitudinal fasciculus fractional anisotropy values correlated with attention and language. Apparent diffusion coefficient values in the left superior longitudinal fasciculus negatively correlated with inhibitory control. In the left arcuate fasciculus, fractional anisotropy correlated with IQ and attention, whereas radial diffusivity values negatively correlated with IQ, fine-motor skills, and expressive language. Findings from this study provide an examination of the relationship between superior longitudinal fasciculus integrity and children's neuropsychological abilities that can be useful in monitoring pediatric neurologic diseases.

### **Determining the Impact of Prenatal Tobacco Exposure on Self-Regulation at 6 Months.**

Wiebe SA, Fang H, Johnson C, James KE, Espy KA. Dev Psychol. 2014 Feb 10. [Epub ahead of print].

The authors' goal in the present study was to examine the effects of maternal smoking during pregnancy on infant self-regulation, exploring birth weight as a mediator and sex as a moderator of risk. A prospective sample of 218 infants was assessed at 6 months of age. Infants completed a battery of tasks assessing working memory/inhibition, attention, and emotional reactivity and regulation. Propensity scores were used to statistically control for confounding risk factors associated with maternal smoking during pregnancy. After prenatal and postnatal confounds were controlled, prenatal tobacco exposure was related to reactivity to frustration and control of attention during stimulus encoding. Birth weight did not mediate the effect of prenatal exposure but was independently related to reactivity and working memory/inhibition. The effect of tobacco exposure was not moderated by sex.

### **Differential Associations between Impulsivity and Risk-taking and Brain Activations Underlying Working Memory in Adolescents**

Panwar K, Rutherford HJ, Mencl WE, Lacadie CM, Potenza MN, Mayes LC. Addict Behav. 2013 Dec 18. pii: S0306-4603(13)00431-0.

Increased impulsivity and risk-taking are common during adolescence and relate importantly to addictive behaviors. However, the extent to which impulsivity and risk-taking relate to brain activations that mediate cognitive processing is not well understood. Here the authors examined the relationships between impulsivity and risk-taking and the neural correlates of working memory. Neural activity was measured in 18 adolescents (13-18 years) while they engaged in a working memory task that included verbal and visuospatial components that each involved encoding, rehearsal and recognition stages. Risk-taking and impulsivity were assessed using the Balloon Analogue Risk Task (BART) and the adolescent version of the Barratt Impulsiveness Scale-11 (BIS-11A), respectively. The authors found overlapping as well as distinct regions subserving the different stages of verbal and visuospatial working memory. In terms of risk-taking, they found a positive correlation between BART scores and activity in subcortical regions (e.g., thalamus, dorsal striatum) recruited during verbal rehearsal, and an inverse correlation between BART scores and cortical regions (e.g., parietal and temporal regions) recruited during visuospatial rehearsal. The BIS-11A evidenced that motor impulsivity was associated with activity in regions recruited during all stages of working memory,

while attention and non-planning impulsivity was only associated with activity in regions recruited during recognition. In considering working memory, impulsivity and risk-taking together, both impulsivity and risk-taking were associated with activity in regions recruited during rehearsal; however, during verbal rehearsal, differential correlations were found. Specifically, positive correlations were found between: (1) risk-taking and activity in subcortical regions, including the thalamus and dorsal striatum; and, (2) motor impulsivity and activity in the left inferior frontal gyrus, insula, and dorsolateral prefrontal cortex. Therefore these findings suggest that while there may be some overlap in the neural correlates of working memory and their relationship to impulsivity and risk-taking, there are also important differences in these constructs and their relationship to the stages of working memory during adolescence.

**Family Obligation Values and Family Assistance Behaviors: Protective and Risk Factors for Mexican-American Adolescents' Substance Use** Telzer EH, Gonzales N, Fuligni AJ. *J Youth Adolesc.* 2014 Feb; 43(2): 270-283.

Adolescent substance use is one of today's most important social concerns, with Latino youth exhibiting the highest overall rates of substance use. Recognizing the particular importance of family connection and support for families from Mexican backgrounds, the current study seeks to examine how family obligation values and family assistance behaviors may be a source of protection or risk for substance use among Mexican-American adolescents. Three hundred and eighty-five adolescents (51% female) from Mexican backgrounds completed a questionnaire and daily diary for 14 consecutive days. Results suggest that family obligation values are protective, relating to lower substance use, due, in part, to the links with less association with deviant peer and increased adolescent disclosure. In contrast, family assistance behaviors are a source of risk within high parent-child conflict homes, relating to higher levels of substance use. These findings suggest that cultural values are protective against substance use, but the translation of these values into behaviors can be a risk factor depending upon the relational context of the family.

**Prenatal Methamphetamine Exposure and Neonatal and Infant Neurobehavioral Outcome: Results from the IDEAL Study** Kiblawi ZN, Smith LM, Diaz SD, Lagasse LL, Derauf C, Newman E, Shah R, Arria A, Huestis M, Haning W, Strauss A, Dellagrotta S, Dansereau LM, Neal C, Lester B. *Subst Abus.* 2014; 35(1):c68-73.

Methamphetamine (MA) use among pregnant women is an increasing problem in the United States. How MA use during pregnancy affects neonatal and infant neurobehavior is unknown. The Infant Development, Environment, and Lifestyle (IDEAL) study screened 34,833 subjects at 4 clinical centers. Of the subjects, 17,961 were eligible and 3705 were consented, among which 412 were enrolled for longitudinal follow-up. Exposed subjects were identified by self-report and/or gas chromatography/mass spectroscopy (GC/MS) confirmation of amphetamine and metabolites in meconium. Comparison subjects were matched (race, birth weight, maternal education, insurance), denied amphetamine use, and had a negative meconium screen. Both groups included prenatal alcohol, tobacco, and marijuana use, but excluded use of opiates, lysergic acid diethylamide, or phencyclidine. The Neonatal Intensive Care Unit (NICU) Network Neurobehavioral Scale (NNNS) was administered within the first 5 days of life and again at 1 month to 380 enrollees (185 exposed, 195 comparisons). Analysis of variance (ANOVA) tested exposure effects on NNNS summary scores at birth and 1 month. General linear model (GLM) repeated-measures analysis assessed the effect of MA exposure over time on the NNNS scores with and without covariates. By 1 month of age, both groups demonstrated higher quality of movement ( $P = .029$ ), less lethargy ( $P = .001$ ), and fewer asymmetric reflexes ( $P = .012$ ), with no significant differences in NNNS scores between the exposed and comparison groups. Over the first month of life, arousal increased in exposed infants but decreased in

comparison infants ( $P = .031$ ) and total stress was decreased in exposed infants, with no change in comparison infants ( $P = .026$ ). Conclusions: Improvement in total stress and arousal were observed in MA-exposed newborns by 1 month of age relative to the newborn period.

**Reactivity and Regulation of Motor Responses in Cocaine-exposed Infants** Fallone MD, Lagasse LL, Lester BM, Shankaran S, Bada HS, Bauer CR. *Neurotoxicol Teratol.* 2014 Feb 28. pii: S0892-0362(14)00023-3.

Effects of prenatal exposure to cocaine on the reactivity and regulation of the motor system of 825 four-month-old infants enrolled in the Maternal Lifestyle Study were examined. Videotaped assessments of 338 cocaine-exposed (CE) infants and 487 non-exposed comparison infants were coded by examiners masked to exposure status. Exposure status was determined by meconium assay and maternal self-report of prenatal cocaine use. Infants were presented with a series of 17 visual, auditory and tactile stimuli for 30-s each. Intensity and latency of limb movement responses on a subset of items were analyzed to test the following hypotheses: CE infants are more active in general; CE infants exhibit increased movement levels for a larger proportion of time in response to stimulation; the motor systems of CE infants are more reactive to stimulation (e.g., shorter latencies to respond); and CE infants are poorer regulators of the motor system. CE infants were not more active in general and data do not indicate a more highly reactive motor system. However, CE infants exhibited increased movement levels for a larger proportion of time in response to stimulation. Additional analysis of movement exhibited during three tactile items found increased movement lability in CE infants and different patterns of responding, suggesting that the effects of prenatal cocaine exposure on the motor system may vary by context. Covariate effects for tobacco, alcohol, and marijuana are also reported.

**Prenatal Methamphetamine Exposure and Neurodevelopmental Outcomes in Children from 1 to 3 Years** Woudes TA, Lagasse LL, Huestis MA, Dellagrotta S, Dansereau LM, Lester BM. *Neurotoxicol Teratol.* 2014 Feb 22. pii: S0892-0362(14)00022-1.

Despite the evidence that women world-wide are using methamphetamine (MA) during pregnancy little is known about the neurodevelopment of their children. The controlled, prospective longitudinal New Zealand (NZ) Infant Development, Environment and Lifestyle (IDEAL) study was carried out in Auckland, NZ. Participants were 103 children exposed to MA prenatally and 107 who were not exposed. The Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) of the Bayley Scales of Infant Development, Second Edition (BSID-II) measured cognitive and motor performances at ages 1, 2 and 3, and the Peabody Developmental Motor Scale, Second Edition (PDMS-II) measured gross and fine motor performances at 1 and 3. Measures of the child's environment included the Home Observation of Measurement of the Environment and the Maternal Lifestyle Interview. The Substance Use Inventory measured maternal drug use. After controlling for other drug use and contextual factors, prenatal MA exposure was associated with poorer motor performance at 1 and 2 years on the BSID-II. No differences were observed for cognitive development (MDI). Relative to non-MA exposed children, longitudinal scores on the PDI and the gross motor scale of the PDMS-2 were 4.3 and 3.2 points lower, respectively. Being male and of Maori descent predicted lower cognitive scores (MDI) and being male predicted lower fine motor scores (PDMS-2). Prenatal exposure to MA was associated with delayed gross motor development over the first 3 years, but not with cognitive development. However, being male and of Maori descent were both associated with poorer cognitive outcomes. Males in general did more poorly on tasks related to fine motor development.

**Risk of Neurobehavioral Disinhibition in Prenatal Methamphetamine-Exposed Young Children with Positive Hair Toxicology Results**

Himes SK, Lagasse LL, Derauf C, Newman E, Smith LM, Arria AM, Della Grotta SA, Dansereau LM, Abar B, Neal CR, Lester BM, Huestis MA. *Ther Drug Monit.* 2014 Feb 7. [Epub ahead of print].

The objective of this study was to evaluate the effects of prenatal methamphetamine exposure (PME) and postnatal drug exposures identified by child hair analysis on neurobehavioral disinhibition at 6.5 years of age. Mother-infant pairs were enrolled in the Infant Development, Environment, and Lifestyle (IDEAL) Study in Los Angeles, Honolulu, Tulsa, and Des Moines. PME was determined by maternal self-report and/or positive meconium results. At the 6.5-year follow-up visit, hair was collected and analyzed for methamphetamine, tobacco, cocaine, and cannabinoid markers. Child behavioral and executive function test scores were aggregated to evaluate child neurobehavioral disinhibition. Hierarchical linear regression models assessed the impact of PME, postnatal substances, and combined PME with postnatal drug exposures on the child's neurobehavioral disinhibition aggregate score. Past year caregiver substance use was compared with child hair results. A total of 264 children were evaluated. Significantly more PME children ( $n = 133$ ) had hair positive for methamphetamine/amphetamine (27.1% versus 8.4%) and nicotine/cotinine (38.3% versus 25.2%) than children without PME ( $n = 131$ ). Overall, no significant differences in analyte hair concentrations were noted between groups. Significant differences in behavioral and executive function were observed between children with and without PME. No independent effects of postnatal methamphetamine or tobacco exposure, identified by positive hair test, were noted and no additional neurobehavioral disinhibition was observed in PME children with postnatal drug exposures, as compared with PME children without postnatal exposure. Child hair testing offered a noninvasive means to evaluate postnatal environmental drug exposure, although no effects from postnatal drug exposure alone were seen. PME, alone and in combination with postnatal drug exposures, was associated with behavioral and executive function deficits at 6.5 years.

**Peers Increase Adolescent Risk Taking Even When the Probabilities of Negative Outcomes Are Known**

Smith AR, Chein J, Steinberg L. *Dev. Psychol.* 2014 Jan 20. [Epub ahead of print].

The majority of adolescent risk taking occurs in the presence of peers, and recent research suggests that the presence of peers may alter how the potential rewards and costs of a decision are valued or perceived. The current study further explores this notion by investigating how peer observation affects adolescent risk taking when the information necessary to make an informed decision is explicitly provided. The authors used a novel probabilistic gambling task in which participants decided whether to play or pass on a series of offers for which the reward and loss outcome probabilities were made explicit. Adolescent participants completed the task either alone or under the belief that they were being observed by an unknown peer in a neighboring room. Participants who believed a peer was observing them chose to gamble more often than participants who completed the task alone, and this effect was most evident for decisions with a greater probability of loss. These results suggest that the presence of peers can increase risk taking among adolescents even when specific information regarding the likelihood of positive and negative outcomes is provided. The findings expand our understanding of how peers influence adolescent decision making and have important implications regarding the value of educational programs aimed at reducing risky behaviors during adolescence.

**Effects of Anonymous Peer Observation on Adolescents' Preference for Immediate Rewards.**

Weigard A, Chein J, Albert D, Smith A, Steinberg L. *Dev Sci.* 2014 Jan; 17(1): 71-78.

Research suggests that the presence of peers influences adolescent risk-taking by increasing the perceived reward value of risky decisions. While prior work has involved observation of participants by their friends, the current study examined whether observation by an anonymous peer could elicit



similarly increased reward sensitivity. Late adolescent participants completed a delay discounting task either alone or under the belief that performance was being observed from a neighboring room by an unknown viewer of the same gender and age. Even in this limited social context, participants demonstrated a significantly increased preference for smaller, immediate rewards when they believed that they were being watched. This outcome challenges several intuitive accounts of the peer effect on adolescent risk-taking, and indicates that the peer influence on reward sensitivity during late adolescence is not dependent on familiarity with the observer. The findings have both theoretical and practical implications for our understanding of social influences on adolescents' risky behavior.

**Within-Adolescent Coupled Changes in Cortisol with DHEA and Testosterone in Response to Three Stressors during Adolescence** Marceau K, Shirtcliff EA, Hastings PD, Klimes-Dougan B, Zahn-Waxler C, Dorn LD, Susman EJ. *Psychoneuroendocrinology*. 2014 Mar; 41: 33-45.

It is hypothesized that hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes function together to maintain adaptive functioning during stressful situations differently in adolescence than the characteristic inverse relations found in adulthood. The authors examined within-person correlated changes (coupling) in cortisol, DHEA and testosterone in response to parent-adolescent conflict discussion, social performance, and venipuncture paradigms. Data are derived from two samples of boys and girls from the Northeastern US (213 adolescents aged 11-16,  $M=13.7$ ,  $SD=1.5$  years; 108 adolescents aged 9-14,  $M=11.99$ ,  $SD=1.55$ ) using different biological sampling vehicles (saliva and blood). Results consistently show that across samples, vehicles, and contexts, cortisol and DHEA and cortisol and testosterone are positively coupled in response to environmental stimuli. Findings underscore the importance of considering the effects of multiple hormones together in order to further our understanding of the biological underpinnings of behavior, especially during adolescence, as adolescence is a developmental transition period that may be qualitatively different from adulthood in terms of hormone functioning.

**Effects of Perceived Racial Discrimination on Health Status and Health Behavior: A Differential Mediation Hypothesis** Gibbons FX, Kingsbury JH, Weng CY, Gerrard M, Cutrona C, Wills TA, Stock M. *Health Psychol*. 2014 Jan; 33(1): 11-19.

Prospective data tested a "differential mediation" hypothesis: The relations (found in previous research) between perceived racial discrimination and physical health status versus health-impairing behavior (problematic substance use) are mediated by two different types of affective reactions, internalizing and externalizing. The sample included 680 African American women from the Family and Community Health Study ( $M$  age = 37 years at Time 1; 45 years at Time 4). Four waves of data were analyzed. Perceived discrimination was assessed, along with anxiety and depression (internalizing) and hostility/anger (externalizing) as mediators, and physical health status and problematic substance use (drinking) as outcomes. Structural equation modeling indicated that discrimination predicted increases in both externalizing and internalizing reactions. These affective responses, in turn, predicted subsequent problematic substance use and physical health status, respectively, also controlling for earlier reports. In each case, the indirect effects from discrimination through the affective mediator to the specific health outcome were significant and consistent with the differential mediation hypothesis. Perceived racial discrimination is associated with increases in internalizing and externalizing reactions among Black women, but these reactions are related to different health outcomes. Changes in internalizing are associated with self-reported changes in physical health status, whereas changes in externalizing are associated with changes in substance use problems. Discussion focuses on the processes whereby discrimination affects health behavior and physical health status.

**Adolescent Risk-taking as a Function of Prenatal Cocaine Exposure and Biological Sex** Allen JW, Bennett DS, Carmody DP, Wang Y, Lewis M. *Neurotoxicol Teratol.* 2014 Jan-Feb; 41: 65-70. The objective of this study was to examine cocaine exposure and biological sex on adolescent risk-taking while controlling for early environmental risk. Adolescents (n=114, mean age=16) were grouped according to high and low risk-taking propensity as measured by the Balloon Analogue Risk Task (BART). Prenatal cocaine exposure was assessed at birth, while environmental risk was assessed at three points during early childhood. A binary regression analysis indicated that males were 3.5 times more likely than females to be high risk-takers. Biological sex and prenatal cocaine exposure interacted such that exposed males were most likely to be high risk-takers while exposed females were the least likely to be high risk-takers. This pattern held after controlling for prenatal alcohol exposure and early environmental risk. Early environmental risk did not predict adolescent risk-taking. These findings complement and extend earlier research demonstrating that prenatal cocaine exposure interacts with biological sex in domains related to inhibitory control, emotion regulation, antisocial behavior, and health risk behaviors during preadolescence.

**Self-Reported Adolescent Behavioral Adjustment: Effects of Prenatal Cocaine Exposure** Min MO, Minnes S, Yoon S, Short EJ, Singer LT. *J Adolesc Health.* 2014 Feb 25. pii: S1054-139X(14)00002-0. The objective of this study was to assess the direct effects of prenatal cocaine exposure (PCE) on adolescent internalizing, externalizing, and attention problems, controlling for confounding drug and environmental factors. At 12 and 15 years of age, 371 adolescents (189 PCE and 182 noncocaine exposed), primarily African-American and of low socioeconomic status, participating in a longitudinal, prospective study from birth were assessed for behavioral adjustment using the Youth Self-Report. Longitudinal mixed model analyses indicated that PCE was associated with greater externalizing behavioral problems at ages 12 and 15 years and more attention problems at age 15, after controlling for confounders. PCE effects were not found for internalizing behaviors. PCE adolescents in adoptive/foster care reported more externalizing and attention problems than PCE adolescents in biological mother/relative care at age 12 or noncocaine-exposed adolescents at both ages. No PCE by gender interaction was found. Prenatal marijuana exposure, home environment, parental attachment and monitoring, family conflict, and violence exposure were also significant predictors of adolescent behavioral adjustment.

**Comparison of 12-year-old Children with Prenatal Exposure to Cocaine and Non-exposed Controls on Caregiver Ratings of Executive Function** Minnes S, Singer LT, Min MO, Lang AM, Ben-Harush A, Short E, Wu M. *J Youth Adolesc.* 2014 Jan; 43(1): 53-69.

Differences in caregiver reported executive function in 12-year-old children who were prenatally exposed to cocaine (PCE) compared to children who were not prenatally exposed to cocaine (NCE) were assessed. One hundred and sixty-nine PCE and 169 NCE, primarily African-American, low socioeconomic status children participated in a prospective longitudinal study. The Behavior Rating Inventory of Executive Function (BRIEF) Parent Form was administered. Two broadband BRIEF scores (Behavioral Regulation Index (BRI) and Metacognition Index (MI)) and a summary Global Executive Composite (GEC) were computed. Multiple and logistic regression analyses were used to assess the effects of amount of PCE on executive function, controlling for covariates including caregiver (rater) psychological distress, child's gender and other prenatal drug exposure variables. After adjustment for covariates, amount of PCE was associated with the GEC and two MI subscales, Plan/Organize and Monitor, with heavier exposure associated with more problems of executive function. An amount of PCE by gender interaction revealed amount of PCE effects in other remaining subscales of the MI (Initiate, Working Memory, and Organization of Materials) only among girls. Head circumference did not mediate the effects of cocaine on outcomes. Higher current caregiver

psychological distress levels were independently associated with poorer ratings on the executive function scales. Assessment and targeted interventions to improve metacognitive processes are recommended for girls who were prenatally exposed to cocaine.

**Prenatal Cocaine Exposure and Trajectories of Externalizing Behavior Problems in Early Childhood: Examining the Role of Maternal Negative Affect** Molnar DS, Levitt A, Eiden RD, Schuetze P. *Dev Psychopathol.* 2014 Mar 12: 1-14.

This study examined the association between prenatal cocaine exposure (PCE) and developmental trajectories of externalizing behavior problems from 18 to 54 months of child age. A hypothesized indirect association between PCE and externalizing trajectories via maternal negative affect was also examined. Caregiving environmental risk and child sex were evaluated as moderators. This study consisted of 196 mother-child dyads recruited at delivery from local area hospitals (107 PCE, 89 non-PCE) and assessed at seven time points across the toddler to preschool periods. Results revealed no direct associations between PCE and externalizing behavior problem trajectories. However, results did indicate that PCE shared a significant indirect relationship with externalizing behavior problem trajectories via higher levels of maternal negative affect. The association between PCE and externalizing problem trajectories was also moderated by caregiving environmental risk such that PCE children in high-risk caregiving environments did not experience the well-documented normative decline in externalizing behavior problems beginning at around 3 years of age. This study suggests potential pathways to externalizing behavior problems among high-risk children.

**Behavior Problems among Cocaine Exposed Children: Role of Physiological Regulation and Parenting** Finger B, Schuetze P, Eiden RD. *Neurotoxicol Teratol.* 2014 Jan 28; 42C: 51-59.

This study examined interrelations between prenatal cocaine exposure, child autonomic regulation, parenting behavior and child sex on parent-reported behavior problems at 36 months of age. The authors hypothesized that respiratory sinus arrhythmia (RSA) at 13 months of age would mediate the relation between cocaine exposure and behavior problems. They also hypothesized that child sex, maternal negative affect, and maternal sensitivity observed at 13 months of age would moderate the relation between RSA and behavior problems. Results revealed that cocaine exposure predicted low baseline RSA and low RSA withdrawal during a negative affect task. Low baseline RSA, in turn, predicted fewer behavior problems offering support for an indirect association between cocaine exposure and behavior problems. The association between baseline RSA and behavior problems was further moderated by maternal negative affect such that high baseline RSA was more strongly related to behavior problems under conditions of high compared to low maternal negative affect. Results also revealed a near significant trend for baseline RSA to be more strongly related to behavior problems among boys than girls. These findings highlight several possible pathways toward behavior problems among cocaine exposed children.

**Empathic Responsivity at 3 Years of Age in a Sample of Cocaine-exposed Children** Schuetze P, Eiden RD, Molnar DS, Colder CD. *Neurotoxicol Teratol.* 2014 Jan 18; 42C:1-8.

This study examined the association between prenatal exposure to cocaine and behavioral and physiological responsivity. Participants were 216 mother-infant dyads (116 cocaine exposed-CE, 100 nonexposed-NCE) recruited at birth. Measures of heart rate (HR) and respiratory sinus arrhythmia (RSA) were obtained during baseline and during a task designed to elicit empathy (exposure to infant crying). When the effects of prenatal cocaine use were examined in the context of polydrug use, results of model testing indicated that lower gestational age, prenatal exposure to cocaine and postnatal exposure to alcohol were each associated with a reduced suppression of RSA during the empathy task.

These findings provide additional support for an association between prenatal cocaine exposure and dysregulation during early childhood during affect-eliciting environmental challenges.

**Longitudinal Trajectories of Sensation Seeking, Risk Taking Propensity, and Impulsivity across Early to Middle Adolescence** Collado A, Felton JW, Macpherson L, Lejuez CW. Addict Behav. 2014 Feb 7. pii: S0306-4603(14)00025-2.

Adolescent substance use and abuse show associations with increases in disinhibitory constructs, including sensation seeking, risk taking propensity, and impulsivity. However, the longitudinal trajectories of these constructs from early to middle adolescence remain largely unknown. Thus, the current study examined these developmental trajectories in 277 adolescents ( $M_{age}=11.00$  at Wave 1), over five consecutive yearly waves. Controlling for age, Hierarchical Linear Modeling analyses showed that sensation seeking increased linearly, whereas risk taking propensity and impulsivity demonstrated curvilinear changes. Specifically, risk taking propensity increased in the first four waves of assessment but did not evidence changes at the last assessment wave. Impulsivity, on the other hand peaked at wave four before subsequently declining. A comparison between females and males and Black and White adolescents suggested that these groups' trajectories were similar. Black adolescents' sensation seeking trajectory differed from adolescents who belonged to the "Other" racial group (i.e., adolescents who neither self-identified as Black or White). Generally, the study findings replicate and extend earlier work indicating that these risk factors increase across early adolescence and begin to level-off during middle adolescence. The importance of understanding the natural course of these core constructs is of great importance for directing future relevant prevention and intervention work.

**A Controlled Family Study of Cannabis Users With and Without Psychosis** Proal AC, Fleming J, Galvez-Buccollini JA, Delisi LE. Schizophr Res. 2014 Jan; 152(1): 283-288.

Cannabis is one of the most highly abused illicit drugs in the world. Several studies suggest a link between adolescent cannabis use and schizophrenia. An understanding of this link would have significant implications for legalization of cannabis and its medicinal value. The present study aims to determine whether familial morbid risk for schizophrenia is the crucial factor that underlies the association of adolescent cannabis use with the development of schizophrenia. Consecutively obtained probands were recruited into four samples: sample 1: 87 non-psychotic controls with no drug use; sample 2: 84 non-psychotic controls with cannabis use; sample 3: 32 patients with a schizophrenia spectrum psychosis with no drug use; sample 4: 76 patients with schizophrenia spectrum psychosis with cannabis use. All cannabis using subjects used this drug during adolescence, and no other substance, with the exception of alcohol. Structured interviews of probands and family informants were used to obtain diagnostic information about probands and all their known relatives. There was an increased morbid risk for schizophrenia in relatives of the cannabis using and non-using patient samples compared with their respective non-psychotic control samples ( $p=.002$ ,  $p<.001$  respectively). There was no significant difference in morbid risk for schizophrenia between relatives of the patients who use or do not use cannabis ( $p=.43$ ). The results of the current study suggest that having an increased familial morbid risk for schizophrenia may be the underlying basis for schizophrenia in cannabis users and not cannabis use by itself.

**Real-time, Contextual Intervention Using Mobile Technology to Reduce Marijuana Use among Youth: A Pilot Study** Shrier LA, Rhoads A, Burke P, Walls C, Blood EA. Addict Behav. 2014 Jan; 39(1): 173-180.

The authors evaluated the feasibility, acceptability, and potential efficacy of MOMENT, an intervention to reduce youth marijuana use that combines brief motivational enhancement therapy with mobile self-monitoring and responsive messaging. At baseline, primary care patients ages 15-24 who

used marijuana frequently (at least 3 times per week) completed a recall assessment, then 1 week of mobile momentary and daily reports on use-related factors. For the intervention, youth participated in two motivational enhancement therapy sessions, during which they identified their top-3 social and emotional triggers for use and discussed healthy ways to manage them. They then completed two weeks of mobile reports. Upon reporting a top-3 trigger for use, desire to use, or recent use, they received a message supporting self-efficacy and prompting consideration of coping strategies. Generalized estimating equations examined changes in momentary-, daily-, and individual-level measures on 3-month recall and mobile assessments. Twenty-seven youth (M=19.2 years, 70% female) enrolled; there were 377-677 momentary and 50-106 daily reports per study phase. Participants reported reading the messages and finding them motivating, being comfortable with participation, and not experiencing the study as burdensome. Although proportion of momentary reports of being in a top-3 trigger context did not change (36%-43%), marijuana desire in a top-3 trigger context and marijuana use after top-3 trigger exposure decreased over the study ( $p<.0001$  and  $p=.03$ , respectively). Daily- and individual-level measures showed similar, non-significant, improvements. The MOMENT intervention appears feasible, well-accepted, and potentially efficacious for youth who use marijuana frequently.

### **Punishment Insensitivity and Impaired Reinforcement Learning in Preschoolers**

Briggs-Gowan MJ, Nichols SR, Voss J, Zobel E, Carter AS, McCarthy KJ, Pine DS, Blair J, Wakschlag LS. *J Child Psychol Psychiatry*. 2014 Feb; 55(2): 154-161.

Youth and adults with psychopathic traits display disrupted reinforcement learning. Advances in measurement now enable examination of this association in preschoolers. The current study examines relations between reinforcement learning in preschoolers and parent ratings of reduced responsiveness to socialization, conceptualized as a developmental vulnerability to psychopathic traits. One hundred and fifty-seven preschoolers (mean age  $4.7 \pm 0.8$  years) participated in a substudy that was embedded within a larger project. Children completed the 'Stars-in-Jars' task, which involved learning to select rewarded jars and avoid punished jars. Maternal report of responsiveness to socialization was assessed with the Punishment Insensitivity and Low Concern for Others scales of the Multidimensional Assessment of Preschool Disruptive Behavior (MAP-DB). Punishment Insensitivity, but not Low Concern for Others, was significantly associated with reinforcement learning in multivariate models that accounted for age and sex. Specifically, higher Punishment Insensitivity was associated with significantly lower overall performance and more errors on punished trials ('passive avoidance'). Impairments in reinforcement learning manifest in preschoolers who are high in maternal ratings of Punishment Insensitivity. If replicated, these findings may help to pinpoint the neurodevelopmental antecedents of psychopathic tendencies and suggest novel intervention targets beginning in early childhood.

## **CLINICAL NEUROSCIENCE RESEARCH**

### **Striatal-Insula Circuits in Cocaine Addiction: Implications for Impulsivity and Relapse Risk**

McHugh MJ, Demers CH, Braud J, Briggs R, Adinoff B, Stein EA. Am J Drug Alcohol Abuse. 2013 Nov; 39(6): 424–432.

Dysregulated striatal functioning coupled with executive control deficits arising from abnormal frontal cortical function are considered key mechanisms in the development and maintenance of cocaine addiction. The same features are thought to underlie high trait impulsivity observed in cocaine-addicted populations. Employing resting state functional connectivity, the current study sought to identify cortico-striatal circuit alterations in cocaine addiction and examine the degree to which circuit connectivity contributes to relapse risk and impulsivity among cocaine-addicted individuals. Whole-brain resting-state functional magnetic resonance imaging connectivity was assessed in 45 cocaine-addicted individuals relative to 22 healthy controls using seed volumes in the left and right caudate, putamen and nucleus accumbens. Cocaine-addicted individuals completed scans in the final week of a 2–4 weeks residential treatment episode. Relapse by day 30 post-discharge served to separate cocaine-addicted individuals into relapse and non-relapse groups. All participants completed the Barratt Impulsivity Scale (BIS-11a). Cocaine-addicted individuals exhibited reduced positive connectivity between the bilateral putamen and posterior insula and right postcentral gyrus. Group differences were primarily driven by reduced connectivity in relapse individuals relative to controls. No relapse versus non-relapse differences emerged. Impulsivity (BIS-11a) was higher in cocaine-addicted participants, an effect that was partially mediated by reduced putamen-posterior insula connectivity in this group. Cocaine addiction, relapse risk and impulsivity were associated with reduced connectivity in putamen-posterior insula/postcentral gyrus circuits implicated in temporal discounting and habitual responding. Findings provide new insight into the neurobiological mechanisms underlying impulsivity and relapse in cocaine addiction

### **Sex Differences in Resting State Neural Networks of Nicotine-dependent Cigarette Smokers**

Wetherill RR, Jagannathan K, Shin J, Franklin TR. Addictive Behaviors. 2014 April; 39(4): 789–792. Although several sex differences in nicotine dependence have been identified, the neural mechanisms underlying these sex differences are not clear. The present study examines sex differences in resting-state brain activity using an arterial spin labeling (ASL) perfusion imaging technique. Fifty-one (31 males) sated nicotine-dependent cigarette smokers underwent perfusion functional magnetic resonance imaging during the resting state. Using functionally defined hippocampus/amygdala (HIP/AMY) seed regions, the authors observed sex differences in correlation strength between the HIP/AMY and the bilateral anterior insula, rostral anterior cingulate cortex, and inferior parietal lobule with females showing stronger functional coupling than males. This pattern of synchronous variations in dynamic cerebral blood flow is consistent with recent models of nicotine dependence, and as such, our findings provide a novel perspective on the neural mechanisms that may contribute to sex differences in nicotine dependence.

### **Robust Changes in Reward Circuitry during Reward Loss in Current and Former Cocaine Users during Performance of a Monetary Incentive Delay Task**

Patela KT, Stevens KT, Med SA, Musk C, Thomas AD, Potenza MN, Pearson GD. Biol Psychiatry. 2013 Oct; 74(7): 529–537. Abnormal function in reward circuitry in cocaine addiction could predate drug use as a risk factor, follow drug use as a consequence of substance-induced alterations, or both. The authors used a functional magnetic resonance imaging monetary incentive delay task (MIDT) to investigate reward-loss neural response differences among 42 current cocaine users, 35 former cocaine users, and 47 healthy subjects who also completed psychological measures and tasks related to impulsivity and

reward. The authors found various reward processing-related group differences in several MIDT phases. Across task phases they found a control > current user > former user activation pattern, except for loss outcome, where former compared with current cocaine users activated ventral tegmental area more robustly. The authors also found regional prefrontal activation differences during loss anticipation between cocaine-using groups. Both groups of cocaine users scored higher than control subjects on impulsivity, compulsivity and reward-punishment sensitivity factors. In addition, impulsivity-related factors correlated positively with activation in amygdala and negatively with anterior cingulate activation during loss anticipation. Compared with healthy subjects, both former and current users displayed abnormal brain activation patterns during MIDT performance. Both cocaine groups differed similarly from healthy subjects, but differences between former and current users were localized to the ventral tegmental area during loss outcome and to prefrontal regions during loss anticipation, suggesting that long-term cocaine abstinence does not normalize most reward circuit abnormalities. Elevated impulsivity-related factors that relate to loss processing in current and former users suggest that these tendencies and relationships may pre-exist cocaine addiction.

**Abstinence-related Changes in Sleep during Treatment for Cocaine Dependence** Angarit GA, Canavana SV, Foreselius E, Bessetta A, Pittman B, Morgan PT. *Drug Alcohol Depend.* 2014 Jan 1; 134: 343-347.

Former sleep studies among non-treatment seeking chronic cocaine users had captured polysomnographic changes for as long as three weeks of abstinence. 20 cocaine dependent participants, randomized to placebo in an ongoing clinical trial, received 12 days of inpatient substance abuse treatment followed by 6 weeks of outpatient cognitive behavioral therapy. Polysomnographic recording was performed on consecutive nights during the 1st and 2nd inpatient and 3rd and 6th outpatient weeks. Number of days abstinent was determined from thrice weekly urine toxicology and self-report. Polysomnographic sleep was compared between study week 1 and 2, using paired *t*-tests. Trajectory of total sleep time (TST) was modeled both as a linear and a quadratic function of days abstinent. Despite reporting an improvement in overall sleep quality, polysomnographic sleep worsened from week 1 to 2. Among all participants, TST and stage 2 sleep time decreased, while REM sleep latency increased. Among participants who began the study with a positive urine test, there was also a decrease in REM and a trend for decreased slow wave sleep. TST compared to number of days abstinent (up to 54 days) was best fit with a quadratic model ( $p = 0.002$ ), suggesting the possibility of an improvement in total sleep time with extended abstinence. This is the first polysomnographic characterization of sleep in a large sample of cocaine users in treatment. Present findings confirm earlier results of poor and deteriorating sleep early in abstinence, and raise the possibility of improvement after an extended abstinence.

**Heroin and Amphetamine Users Display Opposite Relationships between Trait and Neurobehavioral Dimensions of Impulsivity** Vassileva J, Paxton J, Moeller FG, Wilson MJ, Bozgunov K, Martin EM, Gonzalez R, Vasilev G. *Addict Behav.* 2014 Mar; 39(3): 652-659.

The multidimensional construct of impulsivity is implicated in all phases of the addiction cycle. Substance dependent individuals (SDIs) demonstrate elevated impulsivity on both trait and laboratory tests of neurobehavioral impulsivity; however our understanding of the relationship between these different aspects of impulsivity in users of different classes of drugs remains rudimentary. The goal of this study was to assess for commonalities and differences in the relationships between trait and neurobehavioral impulsivity in heroin and amphetamine addicts. Participants included 58 amphetamine dependent (ADIs) and 74 heroin dependent individuals (HDIs) in protracted abstinence. The authors conducted Principal Component Analyses (PCA) on two self-report trait and six neurobehavioral measures of impulsivity, which resulted in two trait impulsivity (action, planning) and four

neurobehavioral impulsivity composites (discriminability, response inhibition efficiency, decision-making efficiency, quality of decision-making). Multiple regression analyses were used to determine whether neurobehavioral impulsivity is predicted by trait impulsivity and drug type. The analyses revealed a significant interaction between drug type and trait action impulsivity on response inhibition efficiency, which showed opposite relationships for ADIs and HDIs. Specifically, increased trait action impulsivity was associated with worse response inhibition efficiency in ADIs, but with better efficiency in HDIs. These results challenge the unitary account of drug addiction and contribute to a growing body of literature that reveals important behavioral, cognitive, and neurobiological differences between users of different classes of drugs.

**Individualized Brain Inhibition and Excitation Profile in Response to Paired-Pulse TMS** Du X, Summerfelt A, Chiappelli J, Holcomb HH, Hong LE. *J Mot Behav.* 2014; 46(1): 39-48.

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are generated from paired-pulse transcranial magnetic stimulations (ppTMS) using certain interstimulus intervals (ISIs). ppTMS provides an accessible technique to evaluate inhibitory and facilitatory motor neural circuits. However, SICI and ICF are highly variable such that individual variability is not captured by any one static ISI. The authors hypothesized that individuals may have individualized and relatively stable pattern of SICI-ICF profiles. They tested SICI and ICF profiles using ISIs from 1 to 500 ms, on 2 occasions about 3 weeks apart, and the test-retest reliability, in 23 healthy controls. Moderate-to-good test-retest reliabilities were found at ppTMS with 1 and 3 ms ISIs (SICI) and with 12, 15, 18, and 21 ms ISIs (ICF), but not with other control ISIs. A similar pattern of results was obtained for men and women. Interestingly, the peak facilitation, peak inhibition, and maximum inhibition and facilitation ranges were individualized, such that they varied considerably across individuals but had high repeatability within individual (Cronbach's  $\alpha = 0.76$  to  $0.85$ ). Therefore, individuals appear to have unique inhibition-facilitation profiles that are relatively stable. Although the functional implications of individualized profiles are currently unknown, the relatively stable profiles may index underlying neural inhibition and excitation traits.

**FAAH Selectively Influences Placebo Effects** Peciña M, Martínez-Jauand M, Hodgkinson C, Stohler CS, Goldman D, Zubieta JK. *Mol Psychiatry.* 2014 Mar; 19(3): 385-391.

Endogenous opioid and cannabinoid systems are thought to act synergistically regulating antinociceptive and reward mechanisms. To further understand the human implications of the interaction between these two systems, we investigated the role of the common, functional missense variant Pro129Thr of the gene coding fatty acid amide hydrolase (FAAH), the major degrading enzyme of endocannabinoids, on psychophysical and neurotransmitter (dopaminergic, opioid) responses to pain and placebo-induced analgesia in humans. FAAH Pro129/Pro129 homozygotes, who constitute nearly half of the population, reported higher placebo analgesia and more positive affective states immediately and 24h after placebo administration; no effects on pain report in the absence of placebo were observed. Pro129/Pro129 homozygotes also showed greater placebo-induced  $\mu$ -opioid, but not D2/3 dopaminergic, enhancements in neurotransmission in regions known involved in placebo effects. These results show that a common genetic variation affecting the function of the cannabinoid system is serving as a probe to demonstrate the involvement of cannabinoid and opioid transmitters on the formation of placebo effects.



**Specifying the Non-specific Factors Underlying Opioid Analgesia: Expectancy, Attention, and Affect** Atlas LY, Wielgosz J, Whittington RA, Wager TD. *Psychopharmacology (Berl)*. 2014 Mar; 231(5): 813-823.

Psychological processes such as expectancy, attention, and affect directly influence clinical outcomes. These factors are grouped together as "nonspecific" factors, or placebo effects, in the medical literature, and their individual contributions are rarely considered. The pain-reducing effects of analgesic treatments may reflect changes in these psychological factors, rather than pure drug effects on pain. Furthermore, drug effects may not be isolated by drug vs. placebo comparisons if drugs interact with relevant psychological processes. The authors sought to determine whether the analgesic effects of opioid and placebo treatment are mediated by changes in attention, expectancy, or affect. They crossed intravenous administration of a potent opioid analgesic, remifentanyl, with information about drug delivery (treatment expectancy or placebo) using a balanced placebo design. They measured drug and treatment expectancy effects on pain, attention, and responses to emotional images. They also examined interactions with cue-based expectations about noxious stimulation or stimulus expectancy. Pain was additively influenced by treatment expectancy, stimulus expectancy, and drug concentration. Attention performance showed a small but significant interaction between drug and treatment expectancy. Finally, remifentanyl enhanced responses to both positive and negative emotional images. The pain-relieving effects of opioid drugs are unlikely to be mediated by changes in threat or affective processing. Standard open-label opioid administration influences multiple clinically relevant cognitive and emotional processes. Psychological factors can combine with drug effects to influence multiple outcomes in distinct ways. The influence of specific psychological factors should be considered when developing and testing pharmacological treatments.

**Endogenous Opioid Inhibition of Chronic Low-back Pain Influences Degree of Back Pain Relief after Morphine Administration** Bruehl S, Burns JW, Gupta R, Buvanendran A, Chont M, Schuster E, France CR. *Reg Anesth Pain Med*. 2014 Mar-Apr; 39(2): 120-125.

Factors underlying differential responsiveness to opioid analgesic medications used in chronic pain management are poorly understood. The authors tested whether individual differences in endogenous opioid inhibition of chronic low-back pain were associated with the magnitude of acute reductions in back pain ratings after morphine administration. In randomized counterbalanced order over three sessions, 50 chronic low-back pain patients received intravenous naloxone (8 mg), morphine (0.08 mg/kg), or placebo. Back pain intensity was rated predrug and again after peak drug activity was achieved using the McGill Pain Questionnaire-Short Form (Sensory and Affective subscales, VAS Intensity measure). Opioid blockade effect measures to index degree of endogenous opioid inhibition of back pain intensity were derived as the difference between predrug to postdrug changes in pain intensity across placebo and naloxone conditions, with similar morphine responsiveness measures derived across placebo and morphine conditions. Morphine significantly reduced back pain compared with placebo (McGill Pain Questionnaire-Short Form Sensory, VAS;  $P < 0.01$ ). There were no overall effects of opioid blockade on back pain intensity. However, individual differences in opioid blockade effects were significantly associated with the degree of acute morphine-related reductions in back pain on all measures, even after controlling for effects of age, sex, and chronic pain duration ( $P < 0.03$ ). Individuals exhibiting greater endogenous opioid inhibition of chronic back pain intensity reported less acute relief of back pain with morphine. Morphine appears to provide better acute relief of chronic back pain in individuals with lower natural opioidergic inhibition of chronic pain intensity. Possible implications for personalized medicine are discussed.

**Attentional Bias for Nondrug Reward is Magnified in Addiction** Anderson BA, Faulkner ML, Rilee JJ, Yantis S, Marvel CL. *Exp Clin Psychopharmacol.* 2013 Dec; 21(6): 499-506.

Attentional biases for drug-related stimuli play a prominent role in addiction, predicting treatment outcomes. Attentional biases also develop for stimuli that have been paired with nondrug rewards in adults without a history of addiction, the magnitude of which is predicted by visual working-memory capacity and impulsiveness. The authors tested the hypothesis that addiction is associated with an increased attentional bias for nondrug (monetary) reward relative to that of healthy controls, and that this bias is related to working-memory impairments and increased impulsiveness. Seventeen patients receiving methadone-maintenance treatment for opioid dependence and 17 healthy controls participated. Impulsiveness was measured using the Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barratt, 1995), visual working-memory capacity was measured as the ability to recognize briefly presented color stimuli, and attentional bias was measured as the magnitude of response time slowing caused by irrelevant but previously reward-associated distractors in a visual-search task. The results showed that attention was biased toward the distractors across all participants, replicating previous findings. It is important to note, this bias was significantly greater in the patients than in the controls and was negatively correlated with visual working-memory capacity. Patients were also significantly more impulsive than controls as a group. These findings demonstrate that patients in treatment for addiction experience greater difficulty ignoring stimuli associated with nondrug reward. This nonspecific reward-related bias could mediate the distracting quality of drug-related stimuli previously observed in addiction.

**Reappraisal and Expected Value Modulate Risk-taking** Braunstein LM, Herrera SJ, Delgado MR. *Cogn Emot.* 2014; 28(1): 172-181.

Decision making is informed by appraisals of appetitive cues and their associated opportunities for rewards. Such appraisals can be modulated by cognitive regulation strategies in order to promote goal-directed choices. Little is known about how cognitive regulation strategies, especially reappraisal, alter risk taking during decision making. To characterize the effect of reappraisal on risk taking, the authors systematically varied both the goal of regulation and the value of the decision options. Participants engaged in two reappraisal strategies with opposite goals, to increase ("emphasize") or decrease ("de-emphasize") the importance of an upcoming decision, during the presentation of cues signaling monetary decisions. The expected value of taking a risk was systematically varied across decisions such that a risky choice could be beneficial or disadvantageous. Reappraisal strategies increased or decreased risk taking in accordance both with regulation goals and expected value information. These results suggest that reappraisal can be used to flexibly alter behavior associated with appetitive cues while maintaining value information.

**Neural Computations Underlying Arbitration Between Model-based and Model-free Learning** Lee SW, Shimojo S, O'Doherty JP. *Neuron.* 2014 Feb 5; 81(3): 687-699.

There is accumulating neural evidence to support the existence of two distinct systems for guiding action selection, a deliberative "model-based" and a reflexive "model-free" system. However, little is known about how the brain determines which of these systems controls behavior at one moment in time. The authors provide evidence for an arbitration mechanism that allocates the degree of control over behavior by model-based and model-free systems as a function of the reliability of their respective predictions. They show that the inferior lateral prefrontal and frontopolar cortex encode both reliability signals and the output of a comparison between those signals, implicating these regions in the arbitration process. Moreover, connectivity between these regions and model-free valuation areas is negatively modulated by the degree of model-based control in the arbitrator, suggesting that arbitration

may work through modulation of the model-free valuation system when the arbitrator deems that the model-based system should drive behavior.

**Cognitive Performance in Methadone Maintenance Patients: Effects of Time Relative to Dosing and Maintenance Dose Level**

Rass O, Kleykamp BA, Vandrey RG, Bigelow GE, Leoutsakos JM, Stitzer ML, Strain EC, Copersino ML, Mintzer MZ. Exp Clin Psychopharmacol. 2014 Feb 17. [Epub ahead of print].

Given the long-term nature of methadone maintenance treatment, it is important to assess the extent of cognitive side effects. This study investigated cognitive and psychomotor performance in 51 methadone maintenance patients (MMP) as a function of time since last methadone dose and maintenance dose level. MMP maintained on doses ranging from 40 to 200 mg (mean = 97 mg) completed a battery of psychomotor and cognitive measures across 2 sessions, during peak and trough states, in a double-blind crossover design. Peak sessions were associated with worse performance on measures of sensory processing, psychomotor speed, divided attention, and working memory, compared with trough sessions. The effects of maintenance dose were mixed, with higher dose resulting in worse performance on aspects of attention and working memory, improved performance on executive function, and no effects on several measures. Longer treatment duration was associated with better performance on some measures, but was also associated with increased sensitivity to time since last dose (i.e., worse performance at peak vs. trough) on some measures. The results suggest that cognitive functioning can fluctuate as a function of time since last dose even in MMP who have been maintained on stable doses for an extended time (mean duration in treatment = 4 years), but worsened performance at peak is limited to a subset of functions and may not be clinically significant at these modest levels of behavioral effect. For patients on stable methadone maintenance doses, maintenance at higher doses may not significantly increase the risk of performance impairment.

**Subjective, Cognitive and Cardiovascular Dose-effect Profile of Nabilone and Dronabinol in Marijuana Smokers**

Bedi G, Cooper ZD, Haney M. Addict Biol. 2013 Sep; 18(5): 872-881.

Marijuana dependence is a substantial public health problem, with existing treatments showing limited efficacy. In laboratory and clinical studies, the cannabinoid receptor 1 agonist oral  $\Delta^9$ tetrahydrocannabinol (THC; dronabinol) has been shown to decrease marijuana withdrawal but not relapse. Dronabinol has poor bioavailability, potentially contributing to its failure to decrease relapse. The synthetic THC analogue, nabilone, has better bioavailability than dronabinol. The authors therefore aimed to characterize nabilone's behavioral and physiological effects across a range of acute doses in current marijuana smokers and compare these with dronabinol's effects. Participants (4 female; 10 male) smoking marijuana 6.6 (standard deviation = 0.7) days/week completed this outpatient, within-subjects, double-blind, randomized protocol. Over seven sessions, the time-dependent subjective, cognitive and cardiovascular effects of nabilone (2, 4, 6, 8 mg), dronabinol (10, 20 mg) and placebo were assessed. Nabilone (4, 6, 8 mg) and dronabinol (10, 20 mg) increased ratings of feeling a good effect, a strong effect and/or 'high' relative to placebo; nabilone had a slower onset of peak subjective effects than dronabinol. Nabilone (6, 8 mg) modestly lowered psychomotor speed relative to placebo and dronabinol. There were dose-dependent increases in heart rate after nabilone, and nabilone (2 mg) and dronabinol (10 mg) decreased systolic blood pressure. Thus, nabilone produced sustained, dose-related increases in positive mood, few cognitive decrements and lawful cardiovascular alterations. It had a longer time to peak effects than dronabinol, and effects were more dose-related, suggesting improved bioavailability. Nabilone was well tolerated by marijuana smokers, supporting further testing as a potential medication for marijuana dependence.

**Elevation of Dopamine Induced by Cigarette Smoking: Novel Insights From a [(11)C]-(+)-PHNO PET Study in Humans** Le Foll B, Guranda M, Wilson AA, Houle S, Rusjan PM, Wing VC, Zawertailo L, Busto U, Selby P, Brody AL, George TP, Boileau I. Neuropsychopharm. 2014 Jan; 39(2): 415-424.

Positron emission tomography (PET) has convincingly provided in vivo evidence that psychoactive drugs increase dopamine (DA) levels in human brain, a feature thought critical to their reinforcing properties. Some controversy still exists concerning the role of DA in reinforcing smoking behavior and no study has explored whether smoking increases DA concentrations at the D3 receptor, speculated to have a role in nicotine's addictive potential. Here, the authors used PET and [(11)C]-(+)-PHNO ([[(11)C]-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9-ol]) to test the hypothesis that smoking increases DA release (decreases [(11)C]-(+)-PHNO binding) in D2-rich striatum and D3-rich extra-striatal regions and is related to craving, withdrawal and smoking behavior. Ten participants underwent [(11)C]-(+)-PHNO scans after overnight abstinence and after smoking a cigarette. Motivation to smoke (smoking topography), mood, and craving were recorded. Smoking significantly decreased self-reported craving, withdrawal, and [(11)C]-(+)-PHNO binding in D2 and D3-rich areas (-12.0 and -15.3%, respectively). The authors found that motivation to smoke (puff rate) predicted magnitude of DA release in limbic striatum, and the latter was correlated with decreased craving and withdrawal symptoms. This is the first report suggesting that, in humans, DA release is increased in D3-rich areas in response to smoking. Results also support the preferential involvement of the limbic striatum in motivation to smoke, anticipation of pleasure from cigarettes and relief of withdrawal symptoms. The authors propose that due to the robust effect of smoking on [(11)C]-(+)-PHNO binding, this radiotracer represents an ideal translational tool to investigate novel therapeutic strategies targeting DA transmission.

**Investigation of Sex-Dependent Effects of Cannabis in Daily Cannabis Smokers** Cooper ZD, Haney M. Drug Alcohol Depend. 2014 Mar 1; 136: 85-91.

Women exhibit an accelerated progression from first cannabis use to cannabis use disorder (CUD) and show pronounced negative clinical issues related to CUD relative to men. Whether sex-dependent differences in cannabis' direct effects contribute to the heightened risk in women is unknown. This analysis directly compared cannabis' abuse-related subjective effects in men and women matched for current cannabis use. Data from four double-blind, within-subject studies measuring the effects of active cannabis (3.27-5.50% THC, depending on study) relative to inactive cannabis (0.00% THC) were combined for this analysis. Data from equal numbers of men and women from each study matched for current cannabis use were pooled (total n=35 men; 35 women); cannabis' effects were analyzed according to cannabis condition (active versus inactive) and sex. Active cannabis produced more robust subjective effects associated with abuse liability ('Good,' 'Liking,' 'Take Again') and intoxication ('High,' 'Stimulated') relative to inactive cannabis ( $p \leq 0.0001$ ). Women reported higher ratings of abuse-related effects ['Take Again' and 'Good' ( $p \leq 0.05$ )] relative to men under active cannabis conditions but did not differ in ratings of intoxication. Active cannabis increased heart rate ( $p \leq 0.0001$ ) equally for both sexes. The results from this study suggest that when matched for cannabis use, women are more sensitive to the subjective effects related to cannabis' abuse liability relative to men, which may contribute to the enhanced vulnerability to developing CUD. Thus, sex is an important variable to consider when assessing the development of CUD.

**Association Between Nicotine Dependence Severity, BOLD Response to Smoking Cues, and Functional Connectivity**

Claus ED, Blaine SK, Filbey FM, Mayer AR, Hutchison KE.

Neuropsychopharm. 2013 Nov; 38(12): 2363-2372.

Enhanced motivational salience towards smoking cues is a consequence of chronic nicotine use, but the degree to which this value increases beyond that of other appetitive cues is unknown. In addition, it is unclear how connectivity between brain regions influences cue reactivity and how cue reactivity and functional connectivity are related to nicotine dependence severity. This study examined neural responses during the presentation of smoking cues and appetitive control cues, as well as functional connectivity in 116 smokers with a range of nicotine dependence severity. Smoking cues elicited greater response above baseline than food cues in orbitofrontal cortex (OFC) and supplementary motor area (SMA) and less deactivation below baseline in middle frontal gyrus, inferior parietal lobe, and middle temporal gyrus. Psychophysiological interaction (PPI) analysis using right OFC as a seed revealed increased connectivity with somatosensory cortex and lateral inferior parietal lobe during smoking cues compared with food cues. Similarly, a PPI analysis using left insula as a seed showed stronger connectivity with somatosensory cortex, right insula, OFC, and striatum. Finally, relationships with nicotine dependence scores showed enhanced response in insula and dorsal anterior cingulate cortex in the smoking vs food comparison, and increased connectivity between insula and circuits involved in motivated behavior. Combined, these results suggest that smokers engage attentional networks and default mode networks involved in self-referential processing to a greater degree during smoking cues. In addition, individuals with greater nicotine dependence severity show increased engagement of sensorimotor and motor preparation circuits, suggesting increased reliance on habitual behavior.

**Safety and Efficacy of Varenicline to Reduce Positive Subjective Effects Produced by Methamphetamine in Methamphetamine-Dependent Volunteers**

Verrico CD, Mahoney JJ 3rd, Thompson-Lake DG, Bennett RS, Newton TF, De La Garza, R 2<sup>nd</sup>. Int J Neuropsychopharm. 2014 Feb; 17(2): 223-233.

Methamphetamine use is increasing in the US. Although there are no Food and Drug Administration (FDA)-approved medications for methamphetamine dependence, preclinical and clinical studies suggest that methamphetamine users may benefit from treatments that enhance cholinergic neurotransmission. Consequently, the authors determined the safety and the efficacy of varenicline treatment, a partial agonist at  $\alpha 4\beta 2$  and a full agonist at  $\alpha 7$  nicotinic acetylcholine receptors, to reduce positive subjective effects produced by smoked methamphetamine. Additionally, the effects of treatment with varenicline on the cardiovascular and reinforcing effects of methamphetamine were determined. The authors conducted a double-blind, placebo-controlled, within-subjects trial of varenicline vs. placebo in methamphetamine-dependent volunteers who were not seeking treatment. Participants were randomly assigned to receive one dose of varenicline (0, 1, or 2 mg) po BID, titrated up to the target dose over days 1-7, during each of three separate inpatient phases. Safety measures included the frequency, duration, severity, and relatedness of adverse events reported. Positive subjective effects included 'Any drug effect', 'High', 'Good effects', 'Stimulated', and 'Drug liking', which were rated by participants before and for 1 h after smoking methamphetamine (0, 10, and 30 mg). There were no serious adverse events and no differences in adverse events reported during the three phases. Varenicline (2 mg) significantly reduced ratings of 'Any drug effect' and 'Stimulated', as well as attenuated ratings of 'High', 'Drug liking', and 'Good effects', produced by methamphetamine (30 mg). The ability of varenicline to attenuate the positive subjective effects of methamphetamine in the laboratory suggests that varenicline should continue to be explored as a treatment for methamphetamine dependence.

**Association of Abstinence-Induced Alterations in Working Memory Function and COMT Genotype in Smokers**

Ashare RL, Valdez JN, Ruparel K, Albelda B, Hopson RD, Keefe JR, Loughhead J, Lerman C. *Psychopharma (Berl)*. 2013 Dec; 230(4): 653-662.

The common methionine (met) for valine (val) at codon 158 (val(158)met) polymorphism in the catechol-O-methyltransferase (COMT) gene has been associated with nicotine dependence, alterations in executive cognitive function, and abstinence-induced working memory deficits in smokers. The authors sought to replicate the association of the COMT val allele with abstinence-induced alterations in working memory-related activity in task-positive (executive control) and task-negative (default mode network) regions. Forty smokers (20 val/val and 20 met/met) performed an N-back task while undergoing blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) on two separate occasions: following 72 h of confirmed abstinence and during smoking as usual. An independent sample of 48 smokers who completed the identical N-back task during fMRI in smoking vs. abstinence for another study was used as a validation sample. Contrary to expectations, genotype by session interactions on BOLD signal in executive control regions (dorsolateral prefrontal cortex and dorsal cingulate/medial prefrontal cortex) revealed significant abstinence-induced reductions in the met/met group, but not the val/val group. Results also revealed that val/val smokers may exhibit less suppression of activation in task-negative regions such as the posterior cingulate cortex during abstinence (vs. smoking). These patterns were confirmed in the validation sample and in the whole-brain analysis, though the regions differed from the a priori regions of interest (ROIs) (e.g., precuneus, insula). The COMT val(158)met polymorphism was associated with abstinence-related working memory deficits in two independent samples of smokers. However, inconsistencies compared to prior findings and across methods (ROI vs. whole-brain analysis) highlight the challenges inherent in reproducing results of imaging genetic studies in addiction.

**Altered Neural Processing of the Need to Stop in Young Adults at Risk for Stimulant**

**Dependence** Harlé KM, Shenoy P, Stewart JL, Tapert SF, Yu AJ, Paulus MP. *The Journal of Neuroscience*. 2014 Dec; 34(13): 4567–4580.

Identification of neurocognitive predictors of substance dependence is an important step in developing approaches to prevent addiction. Given evidence of inhibitory control deficits in substance abusers (Monterosso et al., 2005; Fu et al., 2008; Lawrence et al., 2009; Tabibnia et al., 2011), the authors examined neural processing characteristics in human occasional stimulant users (OSU), a population at risk for dependence. A total of 158 nondependent OSU and 47 stimulant-naïve control subjects (CS) were recruited and completed a stop signal task while undergoing functional magnetic resonance imaging (fMRI). A Bayesian ideal observer model was used to predict probabilistic expectations of inhibitory demand, P(stop), on a trial-to-trial basis, based on experienced trial history. Compared with CS, OSU showed attenuated neural activation related to P(stop) magnitude in several areas, including left prefrontal cortex and left caudate. OSU also showed reduced neural activation in the dorsal anterior cingulate cortex (dACC) and right insula in response to an unsigned Bayesian prediction error representing the discrepancy between stimulus outcome and the predicted probability of a stop trial. These results indicate that, despite minimal overt behavioral manifestations, OSU use fewer brain processing resources to predict and update the need for response inhibition, processes that are critical for adjusting and optimizing behavioral performance, which may provide a biomarker for the development of substance dependence.

**Altered Cingulate and Insular Cortex Activation during Risk-Taking in Methamphetamine Dependence: Losses Lose Impact**

Gowin JL, Stewart JL, May AC, Ball TM, Wittmann M, Tapert SF, Paulus MP. *Addiction*. Feb 2014; 109(2): 237–247.

The aims of this study were to determine if methamphetamine-dependent (MD) individuals exhibit behavioral or neural processing differences in risk-taking relative to healthy comparison participants (CTL). This was a cross-sectional study comparing two groups' behavior on a risk-taking task and neural processing as assessed using functional magnetic resonance imaging (fMRI). The study was conducted in an in-patient treatment center and a research fMRI facility in the United States. Sixty-eight recently abstinent MD individuals recruited from a treatment program and 40 CTL recruited from the community completed the study. The study assessed risk-taking behavior (overall and post-loss) using the Risky Gains Task (RGT), sensation-seeking, impulsivity and blood-oxygenation-level-dependent activation in the brain during the decision phase of the RGT. Relative to CTL, MD displayed decreased activation in the bilateral rostral anterior cingulate cortex (ACC) and greater activation in the left insula across risky and safe decisions ( $P < 0.05$ ). Right mid-insula activation among CTL did not vary between risky and safe decisions, but among MD it was higher during risky relative to safe decisions ( $P < 0.05$ ). Among MD, lower activation in the right rostral ACC ( $r = -0.39$ ,  $P < 0.01$ ) and higher activation in the right mid-insula ( $r = 0.35$ ,  $P < 0.01$ ) during risky decisions were linked to a higher likelihood of choosing a risky option following a loss. Methamphetamine-dependent individuals show disrupted risk-related processing in both anterior cingulate and insula, brain areas that have been implicated in cognitive control and interoceptive processing. Attenuated neural processing of risky options may lead to risk-taking despite experiencing negative consequences.

**Attenuated Insular Processing During Risk Predicts Relapse in Early Abstinent**

**Methamphetamine-Dependent Individuals** Gowin JL, Harlé KM, Stewart JL, Wittmann M, Tapert SF, Paulus MP. *Neuropsychopharmacology*. 2013 Dec. [Epub ahead of print DOI: 10.1038/npp.2013.333].

There is some evidence that neuroimaging can be used to predict relapse among abstinent methamphetamine-dependent (MD) individuals. However, it remains unclear what cognitive and neural processes contribute to relapse. This investigation examined whether insula activation during risk-taking decisions—a process shown to be disrupted in MD—is able to predict susceptibility for relapse. Sixty-eight MD enrolled in a treatment program during early abstinence completed a risk-taking task during functional magnetic resonance imaging. Sixty-three of the sixty-eight individuals were followed up 1 year after the study. Of these, 18 MD reported relapse. The 45 abstinent MD showed patterns of insula activation during risky decisions that resembled those found in prior studies of healthy controls, consisting of lower insula activation during safe decisions paired with higher activation during risky decisions. In contrast, the 18 relapsed MD showed similar insula activation during safe and risky decisions. An increase in one standard deviation in the difference in insula activation between risky and safe choices was associated with a 0.34 odds ratio for relapse at any given time. A median split of insula activation (difference between risky and safe) showed that individuals in the bottom half were two times more likely to relapse. In addition, a model that included several other brain regions increased prediction accuracy compared with insula-based model alone. These results suggest that failure to differentially activate the insula as a function of risk is a part of an altered risk-processing network associated with an increased susceptibility to relapse.

**Neural Correlates of Substance Abuse: Reduced Functional Connectivity between Areas Underlying Reward and Cognitive Control**

Motzkin JC, Baskin-Sommers A, Newman JP, Kiehl KA, Koenigs M. Human Brain Mapping. 2014 Feb; [Epub ahead of print DOI:10.1002/hbm.22474]. Substance use disorders (SUD) have been associated with dysfunction in reward processing, habit formation, and cognitive-behavioral control. Accordingly, neurocircuitry models of addiction highlight roles for nucleus accumbens, dorsal striatum, and prefrontal/anterior cingulate cortex. However, the precise nature of the disrupted interactions between these brain regions in SUD, and the psychological correlates thereof, remain unclear. Here the authors used magnetic resonance imaging to measure rest-state functional connectivity of three key striatal nuclei (nucleus accumbens, dorsal caudate, and dorsal putamen) in a sample of 40 adult male prison inmates (n = 22 diagnosed with SUD; n = 18 without SUD). Relative to the non-SUD group, the SUD group exhibited significantly lower functional connectivity between the nucleus accumbens and a network of frontal cortical regions involved in cognitive control (dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, and frontal operculum). There were no group differences in functional connectivity for the dorsal caudate or dorsal putamen. Moreover, the SUD group exhibited impairments in laboratory measures of cognitive-behavioral control, and individual differences in functional connectivity between nucleus accumbens and the frontal cortical regions were related to individual differences in measures of cognitive-behavioral control across groups. The strength of the relationship between functional connectivity and cognitive control did not differ between groups. These results indicate that SUD is associated with abnormal interactions between subcortical areas that process reward (nucleus accumbens) and cortical areas that govern cognitive-behavioral control.

**Striatum and Insula Dysfunction during Reinforcement Learning Differentiates Abstinent and Relapsed Methamphetamine-Dependent Individuals**

Stewart JL, Connolly CG, May AC, Tapert SF, Wittmann M, Paulus MP. Addiction. 2014 Mar; 109(3): 460–471. Individuals with methamphetamine dependence (MD) exhibit dysfunction in brain regions involved in goal maintenance and reward processing when compared with healthy individuals. The authors examined whether these characteristics also reflect relapse vulnerability within a sample of MD patients. The study design was longitudinal, with functional magnetic resonance imaging (fMRI) and clinical interview data collected at baseline and relapse status collected at 1-year follow-up interview. The study setting was Keck Imaging Center, University of California San Diego, USA. MD patients (n=60) enrolled into an in-patient drug treatment program at baseline. MD participants remaining abstinent at 1-year follow-up (abstinent MD group; n=42) were compared with MD participants who relapsed within this period (relapsed MD group; n=18). Behavioral and neural responses to a reinforcement learning (paper-scissors-rock) paradigm recorded during an fMRI session at time of treatment. The relapsed MD group exhibited greater bilateral inferior frontal gyrus (IFG) and right striatal activation than the abstinent MD group during the learning of reward contingencies (Cohen's d range: 0.60-0.83). In contrast, the relapsed MD group displayed lower bilateral striatum, bilateral insula, left IFG and left anterior cingulate activation than the abstinent MD group (Cohen's d range: 0.90-1.23) in response to winning, tying and losing feedback. Methamphetamine-dependent individuals who achieve abstinence and then relapse show greater inferior frontal gyrus activation during learning, and relatively attenuated striatal, insular and frontal activation in response to feedback, compared with methamphetamine-dependent people who remain abstinent.



**Amphetamine Fails to Alter Cued Recollection of Emotional Images: Study of Encoding, Retrieval, and State-Dependency** Weafer J, Gallo DA, de Wit H. PLoS One. 2014 Feb 27; 9(2):e90423. doi: 10.1371/journal.pone.0090423. eCollection 2014.

Stimulant drugs facilitate both encoding and retrieval of salient information in laboratory animals, but less is known about their effects on memory for emotionally salient visual images in humans. The current study investigated dextroamphetamine (AMP) effects on memory for emotional pictures in healthy humans, by administering the drug only at encoding, only at retrieval, or at both encoding and retrieval. During the encoding session, all participants viewed standardized positive, neutral, and negative pictures from the International Affective Picture System (IAPS). 48 hours later they attended a retrieval session testing their cued recollection of these stimuli. Participants were randomly assigned to one of four conditions (N=20 each): condition AP (20 mg AMP at encoding and placebo (PL) at retrieval); condition PA (PL at encoding and AMP at retrieval); condition AA (AMP at encoding and retrieval); or condition PP (PL at encoding and retrieval). Amphetamine produced its expected effects on physiological and subjective measures, and negative pictures were recollected more frequently than neutral pictures. However, contrary to hypotheses, AMP did not affect recollection for positive, negative, or neutral stimuli, whether it was administered at encoding, retrieval, or at both encoding and retrieval. Moreover, recollection accuracy was not state-dependent. Considered in light of other recent drug studies in humans, this study highlights the sensitivity of drug effects to memory testing conditions and suggests future strategies for translating preclinical findings to human behavioral laboratories.

## **EPIDEMIOLOGY RESEARCH**

**HIV Transmission From Drug Injectors To Partners Who Do Not Inject, and Beyond: Modelling The Potential For A Generalized Heterosexual Epidemic In St. Petersburg, Russia** Mills HL, White E, Colijn C, Vickerman P, Heimer R. Drug Alcohol Depend. 2013; 133(1): 242-247.

HIV infection is prevalent among drug injectors in St. Petersburg and their non-injecting heterosexual partners (PIDUs). There are fears that sexual transmission of HIV from IDUs to PIDUs may portend a self-sustaining, heterosexual epidemic in Russia. The present model combines a network model of sexual partnerships of IDUs and non-IDUs to represent sexual transmission of HIV and a deterministic model for parenteral transmission among IDUs. Behavioral parameters were obtained from a survey of St. Petersburg IDUs and their sexual partners. The authors based their model fits on two scenarios for PIDU prevalence in 2006 (5.6% and 15.1%, calculated excluding and including HCV co-infected PIDUs respectively) and compared predictions for the general population HIV prevalence. Results indicate that sexual transmission could sustain a non-IDU HIV epidemic. The model indicates that general population prevalence may be greater than current estimates imply. Parenteral transmission drives the epidemic and the PIDU bridge population plays a crucial role transferring infection to non-IDUs. The model indicates that the high PIDU prevalence is improbable because of the high risk behavior this implies; the lower prevalence is possible. The model implies that transmission through PIDUs will sustain a heterosexual epidemic, if prevalence among IDUs and PIDUs is as high as survey data suggest. The authors postulate that current estimates of population prevalence underestimate the extent of the HIV epidemic because they are based on the number of registered cases only. Curtailing transmission among injectors and PIDUs will be vital in controlling heterosexual transmission.

**The Entry Of Colombian-Sourced Heroin Into The US Market: The Relationship Between Competition, Price, and Purity** Rosenblum D, Unick GJ, Ciccarone D. Int J Drug Policy. 2014; 25(1): 88-95.

There have been large structural changes in the US heroin market over the past 20 years. Colombian-sourced heroin entered the market in the mid-1990s, followed by a large fall in the price per pure gram and the exit of Asian heroin. By the 2000s, Colombian-sourced heroin had become a monopoly on the east coast and Mexican-sourced heroin a monopoly on the west coast with competition between the two in the middle. The authors estimate the relationship between these changes in competitive market structure on retail-level heroin price and purity. They find that the entry of Colombian-sourced heroin is associated with less competition and a lower price per pure gram of heroin at the national level. However, there is wide variation in changes in market concentration across the US. Controlling for the national fall in the heroin price, more competition in a region or city is associated with a lower price per pure gram.

**Driving After Drug or Alcohol Use by US High School Seniors, 2001–2011** O'Malley PM, Johnston LD. Am J Public Health. 2013; 103:2027–2034. doi:10. 2105/AJPH.2013.301246.

The authors examined prevalence, trends, and correlates of driving or riding after use of drugs or alcohol among US high school seniors from 2001 to 2011. Data come from Monitoring the Future, an annual survey of nationally representative samples of high school seniors. The authors used logistic regressions with data from more than 22 000 respondents to examine multivariate associations with demographic and lifestyle factors. Large numbers of US high school seniors put themselves and others at great risk of harm by driving after using marijuana or other illicit drugs or drinking alcohol or by riding in a vehicle whose driver had used marijuana, other illicit drugs, or alcohol. Driving after drinking has declined in recent years, but driving after use of marijuana has increased. A higher percentage of students reported driving after using marijuana than after having 5 or more

alcoholic drinks. Risky driving and riding behaviors differed little between demographic subgroups but considerably according to lifestyle factors. The authors conclude that stronger efforts are needed to combat adolescent driving under the influence of illicit drugs.

**Towards A Comprehensive Developmental Model Of Cannabis Use Disorders** Blanco C, Rafful C, Wall MM, Ridenour TA, Wang S, Kendler KS. *Addiction*. 2014; 109(2): 284-294

The objective of this study was to develop a comprehensive risk-factor model of cannabis use disorders (CUD) based on Kendler's development model for major depression. Risk factors were divided into five developmental tiers based on Kendler's model of depression (childhood, early adolescence, late adolescence, and adulthood, past year). Hierarchical logistic regression models were used to examine the independent contribution of each risk factor. Separate models were built to predict the lifetime risk of cannabis use and the risk of CUD among those with a history of lifetime risk of cannabis use. Data were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) in the United States. Participants consisted of wave 2 of the NESARC (n=34653). Odds ratios (OR), Adjusted OR (AOR) and confidence intervals (95% CI) were used to determine the risk factors in each tier and with multiple models. After mutually adjusting for the effect of other risk factors, lifetime history of drug use disorder (AOR=4.78, 95% CI=1.53-14.91), past year alcohol use disorders (AOR=6.55, 95% CI=2.54-16.89) and independent (AOR=1.57, 95% CI=1.15-2.14) and dependent (AOR=1.25, 95% CI=1.01-1.55) stressful life events predicted lifetime cannabis use. Impulsivity (AOR=2.18, 95% CI=1.34-3.53), past year alcohol use disorders (AOR=4.09, 95% CI=2.29-7.31), greater number of Axis I disorders (AOR=1.56, 95% CI=1.01-2.40) and social deviance (AOR=1.19, 95% CI=1.08-1.32) independently increased the risk of the development of CUD, whereas religious service attendance (AOR=0.50, 95% CI=0.30-0.85) decreased this risk. In both models, the effect of earlier development tiers was mediated by more proximal ones. There were few gender differences in both models. A modification of Kendler's risk factor model for major depression which stratifies risk factors into five groups (childhood, early adolescence, late adolescence, adulthood, past year) provides a useful foundation for a comprehensive developmental model of cannabis use and cannabis use disorders.

**Identifying Childhood Characteristics That Underlie Premorbid Risk For Substance Use Disorders: Socialization and Boldness** Hicks BM, Iacono WG, McGue M. *Dev Psychopathol*. 2013; 1-17.

The authors utilized a longitudinal twin study (N = 2,510) to identify the child characteristics present prior to initiation of substance use that best predicted later substance use disorders. Two independent traits accounted for the majority of premorbid risk: socialization (conformity to rules and conventional values) and boldness (sociability and social assurance, stress resilience, and thrill seeking). Low socialization was associated with disruptive behavior disorders, parental externalizing disorders, and environmental adversity and exhibited moderate genetic (0.45) and shared environmental influences (0.30). Boldness was highly heritable (0.71) and associated with less internalizing distress and environmental adversity. In combination, these traits exhibited robust associations with adolescent and young adult substance use disorders (R = .48 and .50, respectively) and incremental prediction over disruptive behavior disorders, parental externalizing disorders, and environmental adversity. The results were replicated in an independent sample. Socialization and boldness offer a novel conceptualization of underlying risk for substance use disorders that has the potential to improve prediction and theory with implications for basic research, prevention, and intervention.

**Association Between Cannabis Use, Psychosis, and Schizotypal Personality Disorder: Findings From The National Epidemiologic Survey On Alcohol and Related Conditions** Davis GP,

Compton MT, Wang S, Levin FR, Blanco C. Schizophr Res. 2013; 151(1-3): 197-202.

Studies to date showing an association between cannabis use and schizophrenia-spectrum disorders are of relatively small sample sizes with limitations in generalizability. The present study addresses this gap by examining the relationship between cannabis use and psychotic-like symptoms in a large representative community sample. Data were derived from the 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, Wave 2), a large, nationally representative sample of 34,653 adults from the United States population. The authors evaluated the association between lifetime cannabis use, psychosis, and schizotypal personality features. The prevalence of psychosis and schizotypal personality disorder increased significantly with greater cannabis use in a dose-dependent manner. The associations between cannabis use and psychosis were 1.27 (95% CI 1.03-1.57) for lifetime cannabis use, 1.79 (95% CI 1.35-2.38) for lifetime cannabis abuse, and 3.69 (95% CI 2.49-5.47) for lifetime cannabis dependence. There was a similar dose-response relationship between the extent of cannabis use and schizotypal personality disorder (OR=2.02 for lifetime cannabis use, 95% CI 1.69-2.42; OR=2.83 for lifetime cannabis abuse, 95% CI 2.33-2.43; OR=7.32 for lifetime cannabis dependence, 95% CI 5.51-9.72). Likelihood of individual schizotypal features increased significantly with increased extent of cannabis use in a dose-dependent manner. This is the first population-based study to examine the association between lifetime cannabis use, psychosis, and schizotypal personality traits. These results add to evidence that cannabis use may be a risk factor for psychosis liability.

**Adolescents' Nonmedical Use and Excessive Medical Use Of Prescription Medications and the Identification Of Substance Use Subgroups** Cranford JA, McCabe SE, Boyd CJ. Addict Behav. 2013; 38(11): 2768-2771.

The purpose of this study was to identify subgroups of adolescents based on their past 12 month's use of tobacco, alcohol, marijuana, illicit drugs, and nonmedical use and excessive medical use of prescription medications. A cross-sectional Web-based survey of adolescents from two middle and high school districts in Southeastern Michigan was conducted. The sample included 2,744 middle school (7th and 8th grade) and high school (9th through 12th grade) students. Participants had a mean age of 14.8 years (SD = 1.9 years); 50.4% were female, 64.1% were Caucasian, and 30.6% were African American. Participants completed measures of the past 12 months of substance use, parental monitoring, parental substance use, and internalizing and externalizing problems. Exploratory latent class analysis (LCA) indicated four classes. The largest class was composed of participants with low probabilities of using any substances (low/no use class), and the smallest class was composed of participants with relatively high probabilities of using all substances (multiple substances class). A third class included participants with high probabilities of using tobacco, alcohol, and marijuana (TAM). The fourth class consisted of participants with relatively high probabilities of alcohol use, nonmedical prescription drug use, and excessive medical use of prescription drugs (ANM). Female gender predicted membership in the ANM and multiple substance classes, and parental monitoring, parental substance use problems, internalizing, and externalizing problems uniquely predicted membership in all three high-risk risk classes. Results indicated three high-risk subgroups of adolescents, each characterized by a different pattern of substance use. Two risk groups are characterized by relatively high probabilities of nonmedical use and excessive medical use of prescription medications.

**Novel Psychoactive Drug Use Among Younger Adults Involved In US Nightlife Scenes** Kelly BC, Wells BE, Pawson M, LeClair A, Parsons JT, Golub SA. Drug Alcohol Rev 2013; 32: 588-593; Kelly BC, Wells BE, Pawson M, Leclair A, Parsons JT, Golub S. Drug Alcohol Rev. 2013; 32(6): 588-593. The emergence of novel psychoactive substances has been reported in clinical studies and recent studies of users. The use of these substances in European nightlife scenes is well documented. Little research has been done to identify the prevalence of these drugs among young adults active in other regions. The authors focus their sample on socially active young adults to gain an indication of the prevalence and understanding of demographic factors associated with past year mephedrone ('meph', 'bath salts') and synthetic cannabinoid ('spice', 'K2') use. This study reports on the results of a field-based survey of 1740 patrons at nightlife venues in New York City. Within the sample, 8.2% reported use of synthetic cannabinoids and 1.1% reported the use of mephedrone. Gay and bisexual men reported higher prevalence of mephedrone use. Latinos reported higher prevalence of synthetic cannabinoid use. Multivariate analyses indicate that sexual minority identity is associated with mephedrone use and younger age and Latino ethnicity are associated with synthetic cannabinoid use. The findings suggest that the use of synthetic cannabinoids and mephedrone among adults in US nightlife scenes remains relatively low in comparison with European nightlife scenes, and is low relative to other drug use among young people within these scenes.

**Cumulative and Recent Psychiatric Symptoms As Predictors Of Substance Use Onset: Does Timing Matter?** Cerda M, Bordelois PM, Keyes KM, Galea S, Koenen KC, Pardini D. Addiction. 2013; 108(12): 2119-2128.

The authors examined two questions about the relationship between conduct disorder (CD), depression and anxiety symptoms and substance use onset: (i) what is the relative influence of recent and more chronic psychiatric symptoms on alcohol and marijuana use initiation and (ii) are there sensitive developmental periods when psychiatric symptoms have a stronger influence on substance use initiation? Secondary analysis of longitudinal data from the Pittsburgh Youth Study, a cohort study of boys followed annually from 7 to 19 years of age. Recruitment occurred in public schools in Pittsburgh, Pennsylvania, USA. A total of 503 boys. The primary outcomes were age of alcohol and marijuana use onset. Discrete-time hazard models were used to determine whether (i) recent (prior year); and (ii) cumulative (from age 7 until 2 years prior to substance use onset) psychiatric symptoms were associated with substance use onset. Recent anxiety symptoms [hazard ratio (HR) = 1.10, 95% confidence interval (CI) = 1.03-1.17], recent (HR = 1.59, 95% CI = 1.35-1.87), cumulative (HR = 1.45, 95% CI = 1.03-2.03) CD symptoms, and cumulative depression symptoms (HR = 1.04, 95% CI = 1.01-1.08) were associated with earlier alcohol use onset. Recent (HR = 1.39, 95% CI = 1.22-1.58) and cumulative CD symptoms (HR = 1.38, 95% CI = 1.02-1.85) were associated with marijuana use onset. Recent anxiety symptoms were only associated with alcohol use onset among black participants. Timing matters in the relationship between psychiatric symptoms and substance use onset in childhood and adolescence, and the psychiatric predictors of onset are substance-specific. There is no single sensitive developmental period for the influence of psychiatric symptoms on alcohol and marijuana use initiation.

**Prevalence and Correlates Of Street-Obtained Buprenorphine Use Among Current and Former Injectors In Baltimore, Maryland** Genberg BL, Gillespie M, Schuster CR, Johanson C-E, Astemborski J, Kirk GD, Vlahov D, Mehta SH. Addict Behav. 2013; 38(12): 2868-2873.

There are few systematic assessments of street-obtained buprenorphine use from community-based samples in the United States. The objective of this study was to characterize the prevalence, correlates, and reasons for street-obtained buprenorphine use among current and former injection drug users (IDUs) in Baltimore, Maryland. In 2008, participants of the ALIVE (AIDS Linked to the IntraVenous

Experience) study, a community-based cohort of IDUs, were administered a survey on buprenorphine. Street-obtained buprenorphine represented self-reported use of buprenorphine obtained from the street or a friend in the prior three months. Six hundred and two respondents were predominantly male (65%), African-American (91%), and 30% were HIV-positive. Overall, nine percent reported recent street-obtained buprenorphine use, and only 2% reported using to get high. Among active opiate users, 23% reported recent use of street-obtained buprenorphine. Use of buprenorphine prescribed by a physician, injection and non-injection drug use, use of street-obtained methadone and prescription opiates, homelessness, and opioid withdrawal symptoms were positively associated, while methadone treatment, health insurance, outpatient care, and HIV-infection were negatively associated with recent street-obtained buprenorphine use in univariate analysis. After adjustment, active injection and heroin use were positively associated with street-obtained buprenorphine use. Ninety-one percent reported using street-obtained buprenorphine to manage withdrawal symptoms. While 9% reported recent street-obtained buprenorphine use, only a small minority reported using buprenorphine to get high, with the majority reporting use to manage withdrawal symptoms. There is limited evidence of diversion of buprenorphine in this sample and efforts to expand buprenorphine treatment should continue with further monitoring.

**Parenting and Risk For Mood, Anxiety and Substance Use Disorders: A Study In Population-Based Male Twins** Otowa T, Gardner CO, Kendler KS, Hettema JM. Soc Psychiatry Psychiatr Epidemiol. 2013; 48 (11): 1841-1849.

Previous studies consistently identified a relationship between parenting behavior and psychopathology. In this study, the authors extended prior analyses performed in female twins to a large sample of twins from male-male pairs. They used interview data on 2,609 adult male twins from a population-based twin registry. They examined the association between three retrospectively reported parenting dimensions (coldness, protectiveness, and authoritarianism) and lifetime history of seven common psychiatric and substance use disorders. Using univariate structural equation modeling, They also examined the influence of the genetic and environmental factors on parenting. Examined individually, coldness was consistently associated with risk for a broad range of adult psychopathology. Averaged odds of psychiatric disorders associated with parenting were increased between 26 and 36 %. When the three parenting dimensions were examined together, coldness remained significant for major depression, phobia, and generalized anxiety disorder. Controlling for other disorders, the associations between the parenting dimensions and psychopathology were non-specific. Twin fitting model demonstrated that modest heritability accounted for parenting, whereas most variance resulted from the non-shared environment. Based on the authors' current and prior findings, there is broad similarity in the impact of parenting on adult psychopathology between men and women.

**Are There Differences Between Young African-American and European-American Women In The Relative Influences Of Genetics Versus Environment On Age At First Drink and Problem Alcohol Use?** Sartor CE, Nelson EC, Lynskey MT, Madden PAF, Heath AC, Bucholz KK. Alcohol Clin Exp Res. 2013; 37(11): 1939-1946.

Differences in age at initiation of alcohol use and rates of problem drinking between African Americans and European Americans are well documented, but the association between early and problem use-and distinctions by ethnic group in this association-have yet to be examined in a genetically informative framework. Data were derived from a longitudinal study of female twins in Missouri. The sample was composed of 3,532 twins (13.6% African-American [AA], 86.4% European-American [EA]), who participated in the fourth wave of data collection and reported consumption of at least 1 alcoholic drink over the lifetime. Mean age at Wave 4 was 21.7 (range=18 to

29) years. Twin modeling was conducted to estimate the relative contributions of additive genetic (A), shared environmental (C), and unique environmental (E) factors to variation in age at first drink and problem alcohol use and the cross-phenotype overlap in these influences. Early initiation of alcohol use predicted problem use in EA but not AA women. Separate AA and EA twin models produced substantially different estimates (but not statistically different models) of the relative contributions of A and C to problem alcohol use but similar genetic correlations between the phenotypes. Whereas 33% of the variance in the EA model of problem use was attributed to C, no evidence for C was found in the AA model. Heritability estimates for problem alcohol use were 41% in the AA model, 21% in the EA model. Evidence for A and C were found in both AA and EA models of age at first drink, but the A estimate was higher in the EA than AA model (44% vs. 26%). Findings are suggestive of distinctions between AA versus EA women in the relative contribution of genetic and environmental influences on the development of problem drinking.

**Delineating Selection and Mediation Effects Among Childhood Personality and Environmental Risk Factors in the Development of Adolescent Substance Abuse**

Hicks BM, Johnson W, Durbin CE, Blonigen DM, Iacono WG, McGue M. *J Abnorm Child Psychol.* 2013.

Utilizing the large, longitudinal Minnesota Twin Family Study (N=2510; 96 % European American ancestry), the authors examined the influence of several person-environment transactions on adolescent substance abuse. They focused on the two childhood personality traits found to be most predictive of substance abuse in this sample-socialization (willingness to follow rules and endorse conventional values) and boldness (social engagement and assurance, stress resilience, thrill seeking)-and the environmental variables of antisocial and prosocial peers, academic engagement, parent-child relationship quality, and stressful life events. Path analysis revealed that low socialization had a selection effect for each environmental risk factor, that is, socialization at age 11 predicted environmental risk at age 14, after controlling for the stability of the environmental variables from ages 11 to 14. Antisocial peers and academic engagement at age 14 then mediated some of the risk of low socialization on substance abuse at age 17, but the majority of risk for substance abuse was accounted for by the stability of socialization from age 11 to 14. Boldness at age 11 also increased risk for substance abuse, but did so primarily via a direct effect. The findings help to parse the nature of person-environment transactions across multiple personality traits and contextual risk factors that contribute to adolescent substance abuse.

**The Effects Of Exposure To Violence and Victimization Across Life Domains On Adolescent Substance Use**

Wright EM, Fagan AA, Pinchevsky GM. *Child Abuse Negl.* 2013; 37(11): 899-909.

This study uses longitudinal data from the Project on Human Development in Chicago Neighborhoods (PHDCN) to examine the effects of exposure to school violence, community violence, child abuse, and parental intimate partner violence (IPV) on youths' subsequent alcohol and marijuana use. The authors also examine the cumulative effects of being exposed to violence across these domains. Longitudinal data were obtained from 1,655 adolescents and their primary caregivers participating in the PHDCN. The effects of adolescents' exposure to various forms of violence across different life domains were examined relative to adolescents' frequency of alcohol and marijuana use three years later.

Multivariate statistical models were employed to control for a range of child, parent, and family risk factors. Exposure to violence in a one-year period increased the frequency of substance use three years later, though the specific relationships between victimization and use varied for alcohol and marijuana use. Community violence and child abuse, but not school violence or exposure to IPV, were predictive of future marijuana use. None of the independent measures of exposure to violence significantly predicted future alcohol use. Finally, the accumulation of exposure to violence across life domains was detrimental to both future alcohol and marijuana use. The findings support prior research indicating

that exposure to multiple forms of violence, across multiple domains of life, negatively impacts adolescent outcomes, including substance use. The findings also suggest that the context in which exposure to violence occurs should be considered in future research, since the more domains in which youth are exposed to violence, the fewer "safe havens" they have available. Finally, a better understanding of the types of violence youth encounter and the contexts in which these experiences occur can help inform intervention efforts aimed at reducing victimization and its negative consequences.

**Normative Perceptions and Past-Year Consequences As Predictors Of Subjective Evaluations and Weekly Drinking Behavior** Merrill JE, Read JP, Colder CR. *Addict Behav.* 2013; 38(11): 2625-2634.

Problem drinking during the college years continues to be an important area of study. Subjective evaluations of consequences have recently been demonstrated to predict future drinking behavior; however, what predicts those evaluations is yet unknown. Social Learning Theory (SLT) provides a guiding framework in this study. Primary aims are to investigate whether individual differences in past experience with alcohol consequences and normative perceptions of alcohol consequences predict subjective evaluations (i.e., the extent to which consequences are perceived as negative, aversive, or severe) and weekly drinking behavior. The authors also test whether evaluations mediate the influence of past consequences and norms on weekly drinking behavior. Following a baseline assessment, participants (N = 96 regularly drinking college students, 52% female) completed ten weekly web-based surveys on previous week alcohol use, consequences, and subjective evaluations of those consequences. A series of hierarchical linear models were used to test hypotheses. Most mediational pathways were not supported - weekly level evaluations do not appear to fully explain the effect of norms or past experience on weekly level drinking behavior. However, results demonstrated that normative perceptions of and past experience with consequences were associated with both weekly drinking behavior and subjective evaluations, and evaluations remained significant predictors of alcohol use behavior after accounting for these important between-person influences. Findings support the importance placed by SLT on cognition in drinking behavior, and suggest that norms for consequences and subjective evaluations may be appropriate targets of intervention in college students.

**Under Treatment Of Pain: A Prescription For Opioid Misuse Among The Elderly?** Levi-Minzi MA, Surratt HL, Kurtz SP, Buttram ME. *Pain Med.* 2013; 14(11): 1719-1729.

The objective of this study was to examine the demographic, physical, and mental health characteristics; current drug use patterns; motivations for use; and diversion sources among elderly prescription opioid misusers. The research was conducted in research field offices or senior or community center offices in South Florida. Individuals aged 60 and over reporting past 90-day prescription medication misuse served as subjects; only prescription opioid misusers (N = 88) were included in the final analysis. The Global Appraisal of Individual Needs was the main survey instrument. A subsample of elderly reporting substantial prescription drug misuse were chosen for the in-depth interview (N = 30). The mean age was 63.3. Fifty percent reported ever being admitted to a drug treatment program; several endorsed recent illicit drug use: powder cocaine and/or crack (35.2%), marijuana (30.7%), heroin (14.8%). The majority reported past year severe physical pain and discomfort (86.4%), and misuse of their primary opioid for pain (80.7%); over half (52.3%) obtained their primary opioid from their regular doctor. Qualitative data highlight the misuse of prescription opioids due to untreated or undertreated pain. Participants with primary opioid misuse for pain had over 12 times higher odds of obtaining the medication from their regular doctor (odds ratio [OR] = 12.22, P = 0.002) and had lower odds of using a dealer (OR = 0.20, P = 0.005). Findings suggest that this group of elderly participants often misuse their own prescriptions for pain management. This study



highlights the need to educate prescribing professionals on appropriate pain management for older adults while still being sensitive to issues of substance abuse and dependence.

### **The Aftermath Of Public Housing Relocation: Relationship To Substance Misuse**

Cooper HL, Bonney LE, Ross Z, Karnes C, Hunter-Jones J, Kelley ME, Rothenberg R. Drug Alcohol Depend. 2013; 133(1): 37-44.

Several cross-sectional studies have examined relationships between neighborhood characteristics and substance misuse. Using data from a sample of African-American adults relocating from U.S. public housing complexes, the authors examined relationships between changes in exposure to local socioeconomic conditions and substance misuse over time. They tested the hypothesis that adults who experienced greater post-relocation improvements in local economic conditions and social disorder would have a lower probability of recent substance misuse. Data were drawn from administrative sources to describe the census tracts where participants lived before and after relocating. Data on individual-level characteristics, including binge drinking, illicit drug use, and substance dependence, were gathered via survey before and after the relocations. Multilevel models were used to test hypotheses. Participants (N=172) experienced improvements in tract-level economic conditions and, to a lesser degree, in social disorder after moving. A one standard-deviation improvement in tract-level economic conditions was associated with a decrease in recent binge drinking from 34% to 20% ( $p=0.04$ ) and with a decline in using illicit drugs weekly or more from 37% to 16% ( $p=0.02$ ). A reduction in tract-level alcohol outlet density of  $>3.0$  outlets per square mile predicted a reduction in binge drinking from 32% to 18% at  $p=0.05$  significance level. The authors observed relationships between improvements in tract-level conditions and declines in substance misuse, providing further support for the importance of the local environment in shaping substance misuse. These findings have important implications for public housing policies and future research.

### **Risk Factors For Progression To Regular Injection Drug Use Among Street-Involved Youth In A Canadian Setting**

Debeck K, Kerr T, Marshall BDL, Simo A, Montaner J, Wood E. Drug Alcohol Depend. 2013; 133(2): 468-472.

Street-involved youth are at high risk for experimenting with injection drug use; however, little attention has been given to identifying the factors that predict progression to on-going injecting. Logistic regression was used to identify factors associated with progression to injecting weekly on a regular basis among a Canadian cohort of street-involved youth. Among our sample of 405 youth who had initiated injecting at baseline or during study observation, the median age was 22 years (interquartile range [IQR]=21-24), and 72% (293) reported becoming a regular injector at some point after their first injection experience. Of these, the majority ( $n=186$ , 63%) reported doing so within a month of initiating injection drug use. In multivariate analysis, the drug used at the first injection initiation event (opiates vs. cocaine vs. methamphetamine vs. other; all  $p>0.05$ ) was not associated with progression; however, younger age at first injection (adjusted odds ratio [AOR]=1.13), a history of childhood physical abuse (AOR=1.81), prior regular use of the drug first injected (AOR=1.77), and having a sexual partner present at the first injection event (AOR=2.65) independently predicted progression to regular injecting. These data highlight how quickly youth progress to become regular injectors after experimentation. Findings indicate that addressing childhood trauma and interventions such as evidence-based youth focused addiction treatment that could prevent or delay regular non-injection drug use, may reduce progression to regular injection drug use among this population.

**Illicit and Nonmedical Drug Use Among Asian Americans, Native Hawaiians/Pacific Islanders, and Mixed-Race Individuals** Wu L-T, Blazer DG, Swartz MS, Burchett B, Brady KT, NIDA AAPI Workgroup. Drug Alcohol Depend. 2013; 133(2): 360-367.

The racial/ethnic composition of the United States is shifting rapidly, with non-Hispanic Asian-Americans, Native Hawaiians/Pacific Islanders (NHs/PIs), and mixed-race individuals the fastest growing segments of the population. The authors determined new drug use estimates for these rising groups. Prevalence among Whites were included as a comparison. Data were from the 2005-2011 National Surveys on Drug Use and Health. Substance use among respondents aged 12 years was assessed by computer-assisted self-interviewing methods. Respondents' self-reported race/ethnicity, age, gender, household income, government assistance, county type, residential stability, major depressive episode, history of being arrested, tobacco use, and alcohol use were examined as correlates. The authors stratified the analysis by race/ethnicity and used logistic regression to estimate odds of drug use. Prevalence of past-year marijuana use among Whites increased from 10.7% in 2005 to 11.6-11.8% in 2009-2011 ( $P < 0.05$ ). There were no significant yearly changes in drug use prevalence's among Asian-Americans, NHs/PIs, and mixed-race people; but use of any drug, especially marijuana, was prevalent among NHs/PIs and mixed-race people (21.2% and 23.3%, respectively, in 2011). Compared with Asian-Americans, NHs/PIs had higher odds of marijuana use, and mixed-race individuals had higher odds of using marijuana, cocaine, hallucinogens, stimulants, sedatives, and tranquilizers. Compared with Whites, mixed-race individuals had greater odds of any drug use, mainly marijuana, and NHs/PIs resembled Whites in odds of any drug use. Findings reveal alarmingly prevalent drug use among NHs/PIs and mixed-race people. Research on drug use is needed in these rising populations to inform prevention and treatment efforts.

**Nicotinic Receptor Gene Variants Interact With Attention Deficient Hyperactive Disorder Symptoms To Predict Smoking Trajectories From Early Adolescence To Adulthood.** Lee C-T,

Fuemmeler BF, McClernon FJ, Ashley-Koch A, Kollins SH. Addict Behav. 2013; 38(11): 2683-2689. The objective of this study was to examine the association of single nucleotide polymorphisms (SNPs) of the CHRNA6 (rs13280604) and CHRNA6 (rs892413) nicotinic acetylcholine receptor (nAChR) genes and symptoms of attention deficit hyperactivity disorder (ADHD) in predicting smoking patterns from early adolescence to adulthood. A longitudinal cohort of 1137 unrelated youths from the National Longitudinal Study of Adolescent Health provided responses to four surveys from Waves I to IV, and a genetic sample in Wave III. Growth mixture modeling was used to identify smoking patterns and to assess the effects of the two SNPs and ADHD symptoms on cigarette use over time. There were significant main effects of ADHD symptoms and CHRNA6 variants in predicting the number of cigarettes smoked and the pattern of use over time, respectively. There were no main effects of the CHRNA6 variants. However, a significant CHRNA6 variant ADHD symptom interaction was observed, such that individuals with elevated ADHD symptoms and a particular CHRNA6 variant were at increased risk of cigarette use over time. These findings demonstrate that a SNP in a nicotinic receptor gene may interact with ADHD symptoms to link with increased cigarette use across adolescence and young adulthood. Unique associations between specific variants and patterns of ADHD symptoms were identified which may be useful for targeting prevention efforts to individuals at greatest risk for cigarette smoking.

**The Role Of Behavioral Inhibition and Behavioral Approach Systems In The Associations Between Mood and Alcohol Consequences In College: A Longitudinal Multilevel Analysis**

Wardell JD, Read JP, Colder CR. Addict Behav. 2013; 38(11): 2772-2781.

The behavioral inhibition system (BIS) and behavioral approach system (BAS) are thought to influence sensitivity to reinforcement and punishment, making them useful for predicting mood-related

drinking outcomes. This study provided the first examination of BIS and BAS as moderators of longitudinal within-person associations between mood and alcohol-related consequences in college student drinkers. Participants (N = 637) at two public U.S. universities completed up to 14 online surveys over the first three years of college assessing past-month general positive and negative moods, as well as past-month alcohol use and consequences. BIS and BAS were assessed at baseline. Using multilevel regression, the authors found that BIS and BAS moderated the within-person associations between negative mood and alcohol consequences. For students high on BIS only, high on BAS only, or high on both BIS and BAS, within-person increases in negative mood were associated with greater alcohol consequences in the first year of college. However, these negative mood-alcohol consequence associations diminished over time for students high on BIS and low on BAS, but remained strong for students high on both BIS and BAS. Within-person associations between positive mood and alcohol consequences changed from slightly positive to slightly negative over time, but were not moderated by BIS or BAS. Findings suggest that BIS and BAS impact the within-person association between general changes in negative mood and negative alcohol consequences, working jointly to maintain this relationship over time.

**The Latent Structure and Predictors Of Non-Medical Prescription Drug Use and Prescription Drug Use Disorders: A National Study** Blanco C, Rafful C, Wall MM, Jin CJ, Kerridge B, Schwartz RP. *Drug Alcohol Depend.* 2013; 133(2): 473-479.

Despite growing concerns about non-medical prescription drug use and prescription drug use disorders, whether vulnerability for these conditions is drug-specific or occurs through a shared liability and common risk factors is unknown. Exploratory and confirmatory factor analysis of Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions were used to examine the latent structure of non-medical prescription drug use and prescription drug use disorders. Multiple Indicators Multiple Causes (MIMIC) analysis was used to examine whether the effect of sociodemographic and psychiatric covariates occurred through the latent factor, directly on each drug class or both. A one-factor model described well the structure of both non-medical prescription drug use and prescription drug use disorders. Younger age, being White, having more intense pain or one of several psychiatric disorders increased the risk of non-medical prescription drug use through the latent factor. The same covariates, except for anxiety disorders also significantly increased the risk of prescription drug use disorders through the latent factor. Older age directly increased the risk of non-medical use of sedatives, and alcohol use disorders decreased the risk of non-medical tranquilizer use. No covariates had direct effects on the risk of any prescription drug use disorders beyond their effect through the latent factor. The risk for non-medical prescription drug use and prescription drug use disorders occurs through a shared liability. Treatment, prevention and policy approaches directed at these drugs as a group maybe more effective than those focused on individual classes of drugs.

**The Role Of Constraint In the Development Of Nicotine, Marijuana, and Alcohol Dependence In Young Adulthood** Vrieze SI, Vaidyanathan U, Hicks BM, Iacono WG, McGue M. *Behav Genet.* 2014; 44(1):14-24.

The personality-related construct of behavioral disinhibition is hypothesized to confer a generalized risk for alcohol and drug dependence. On average, rates of substance use and scores on measures of disinhibition peak in adolescence and decline as people mature into adulthood. The present study investigated this developmental change by evaluating the relationship between disinhibition and substance use disorders using a longitudinal study of 2,608 twins assessed at ages 17, 24, and 29. These ages include the period of highest risk for substance use disorders (ages 17-24) as well as when substance dependence symptoms typically decline (ages 24-29). Disinhibition was measured with the Multidimensional Personality Questionnaire higher-order scale of Constraint, as well as its constituent

facet scales of Harm Avoidance, Control, and Traditionalism. Constraint's relationship with substance dependence was statistically significant but small and largely genetic, with the genetic relationship declining from adolescence into adulthood. However, this result appeared to be almost entirely driven by Traditionalism, a propensity to hold traditional moral and social values, and not an obvious component of behavioral disinhibition. The results suggest that personality measures of Control and Harm Avoidance play only a small role in the development of substance dependence during late adolescence, and previous findings linking personality measures of disinhibition and substance use may be driven significantly by social and moral values than deficits in impulse control.

**Parental Separation and Early Substance Involvement: Results From Children Of Alcoholic and Cannabis Dependent Twins** Waldron M, Grant JD, Bucholz KK, Lynskey MT, Slutske WS, Glowinski AL, Henders A, Statham DJ, Martin NG, Heath AC. Drug Alcohol Depend. 2014; 134: 78-84.

Risks associated with parental separation have received limited attention in research on children of parents with substance use disorders. The authors examined early substance involvement as a function of parental separation during childhood and parental alcohol and cannabis dependence. Data were drawn from 1318 adolescent offspring of monozygotic (MZ) or dizygotic (DZ) Australian twin parents. Cox proportional hazards regression analyses were conducted predicting age at first use of alcohol, first alcohol intoxication, first use and first regular use of cigarettes, and first use of cannabis, from parental separation and both parent and cotwin substance dependence. Parent and cotwin alcohol and cannabis dependence were initially modeled separately, with post hoc tests for equality of effects. With few exceptions, risks associated with parental alcohol versus cannabis dependence could be equated, with results largely suggestive of genetic transmission of risk from parental substance (alcohol or cannabis) dependence broadly defined. Controlling for parental substance dependence, parental separation was a strong predictor for all substance use variables, especially through age 13. Together, findings underscore the importance of parental separation as a risk-factor for early substance involvement over and above both genetic and environmental influences specific to parental alcohol and cannabis dependence.

**Psychiatric, Psychosocial, and Physical Health Correlates Of Co-Occurring Cannabis Use Disorders and Nicotine Dependence** Peters EN, Schwartz RP, Wang S, O'Grady KE, Blanco C. Drug Alcohol Depend. 2014; 134: 228-234.

Several gaps in the literature on individuals with co-occurring cannabis and tobacco use exist, including the extent of psychiatric, psychosocial, and physical health problems. The authors examine these gaps in an epidemiological study, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), of a large, nationally representative sample. The sample was drawn from Wave 2 NESARC respondents (N=34,653). Adults with current cannabis use disorders and nicotine dependence (CUD+ND) (n=74), CUD only (n=100), and ND only (n=3424) were compared on psychiatric disorders, psychosocial correlates (e.g., binge drinking; partner violence), and physical health correlates (e.g., medical conditions). Relative to those with CUD only, respondents with CUD+ND were significantly more likely to meet criteria for bipolar disorder, Clusters A and B personality disorders, and narcissistic personality disorder, and reported engaging in a significantly higher number of antisocial behaviors. Relative to those with ND only, respondents with CUD+ND were significantly more likely to meet criteria for bipolar disorder, anxiety disorders, and paranoid, schizotypal, narcissistic, and borderline personality disorders; were significantly more likely to report driving under the influence of alcohol and being involved in partner violence; and reported engaging in a significantly higher number of antisocial behaviors. CUD+ND was not associated with physical

health correlates. Poor treatment outcomes for adults with co-occurring cannabis use disorders and nicotine dependence may be explained in part by differences in psychiatric and psychosocial problems.

**Functional Imaging Of Implicit Marijuana Associations During Performance On An Implicit Association Test (IAT)** L Ames S, Grenard JL, W Stacy A, Xiao L, He Q, Wong SW, Xue G, W Wier R, Bechara A. Behav Brain Res. 2013; 256: 494-502.

This research evaluated the neural correlates of implicit associative memory processes (habit-based processes) through the imaging (fMRI) of a marijuana Implicit Association Test. Drug-related associative memory effects have been shown to consistently predict level of drug use. To observe differences in neural activity of associative memory effects, this study compared 13 heavy marijuana users and 15 non-using controls, ranging in age from 18 to 25, during performance of marijuana Implicit Association Test (IAT). Group by condition interactions in the putamen, caudate, and right inferior frontal gyrus were observed. Relative to non-users, marijuana users showed greater bilateral activity in the dorsal striatum (caudate and putamen) during compatible trials focused on perceived positive outcomes of use. Alternatively, relative to the marijuana-using group, the non-users showed greater activity in the right inferior frontal gyrus during incompatible trials, which require more effortful processing of information. Further, relative to fixation, heavy users showed bilateral activity in the caudate and putamen, hippocampus and some frontal regions during compatible trials and no significant activity during incompatible trials. The non-using group showed greater activity in frontal regions during incompatible trials relative to fixation and no significant activity during compatible trials. These findings are consistent with a dual process framework of appetitive behaviors proposing that (1) implicit associations underlying habit are mediated through neural circuitry dependent on the striatum, and (2) deliberative/controlled behaviors are mediated through circuitry more dependent on the prefrontal cortex.

**Correlates Of Elevated Interleukin-6 and C-Reactive Protein In Persons With Or At High Risk For HCV and HIV Infections** Salter ML, Lau B, Mehta SH, Go VF, Leng S, Kirk GD. J Acquir Immune Defic Syndr. 2013; 64(5): 488-495.

HIV and hepatitis C virus (HCV) infections may increase interleukin-6 (IL-6) and C-reactive protein (CRP). However, relationships between inflammatory biomarkers, chronic viral infections, clinical factors, and behavioral factors remain poorly understood. Using linear regression, the authors modeled cross-sectional associations between loge IL-6 or loge CRP levels and HCV, HIV, injection drug use, and comorbidity among 1191 injection drug users. Mean age was 47 years, 46.0% reported currently injecting drugs, 59.0% were HCV mono infected, and 27% were HCV/HIV co-infected. In multivariable models, higher loge IL-6 was associated with HCV mono infection [ $* = 0.191$ , 95% confidence interval (CI): 0.043 to 0.339] and HCV/HIV co-infection ( $* = 0.394$ , 95% CI: 0.214 to 0.574). In contrast, HCV mono infection ( $* = -0.523$ , 95% CI: -0.275 to -0.789) and HCV/HIV co-infection ( $* = -0.554$  95% CI: -0.260 to -0.847) were associated with lower CRP. Lower CRP with HCV infection was independent of liver fibrosis severity, synthetic function, or liver injury markers; CRP decreased with higher HCV RNA. Increased injection intensity was associated with higher IL-6 ( $P = 0.003$ ) and CRP ( $P < 0.001$ ); increasing comorbidity ( $P < 0.001$ ) and older age ( $P = 0.028$ ) were associated with higher IL-6; older age was associated with higher CRP among HCV-uninfected participants ( $P = 0.021$ ). HIV and HCV infections contribute to chronic inflammation; however, reduced CRP possibly occurs through HCV-mediated mechanisms. Findings highlight potentially modifiable contributors to inflammation.

### **Dynamics Of Viral Evolution and Neutralizing Antibody Response After HIV-1 Superinfection**

Chaillon A, Wagner GA, Hepler NL, Little SJ, Kosakovsky Pond SL, Caballero G, Pacold ME, Phung P, Wrinn T, Richman DD, Wertheim JO, Smith DM. J Virol. 2013; 8(23): 12737-12744.

Investigating the incidence and prevalence of HIV-1 superinfection is challenging due to the complex dynamics of two infecting strains. The superinfecting strain can replace the initial strain, be transiently expressed, or persist along with the initial strain in distinct or in recombined forms. Various selective pressures influence these alternative scenarios in different HIV-1 coding regions. The authors hypothesized that the potency of the neutralizing antibody (NAb) response to autologous viruses would modulate viral dynamics in *env* following superinfection in a limited set of superinfection cases. HIV-1 *env* pyro sequencing data were generated from blood plasma collected from 7 individuals with evidence of superinfection. Viral variants within each patient were screened for recombination, and viral dynamics were evaluated using nucleotide diversity. NAb responses to autologous viruses were evaluated before and after superinfection. In 4 individuals, the superinfecting strain replaced the original strain. In 2 individuals, both initial and superinfecting strains continued to co-circulate. In the final individual, the surviving lineage was the product of interstrain recombination. NAb responses to autologous viruses that were detected within the first 2 years of HIV-1 infection were weak or absent for 6 of the 7 recently infected individuals at the time of and shortly following superinfection. These 6 individuals had detectable on-going viral replication of distinct superinfecting virus in the *env* coding region. In the remaining case, there was an early and strong autologous NAb response, which was associated with extensive recombination in *env* between initial and superinfecting strains. This extensive recombination made superinfection more difficult to identify and may explain why the detection of superinfection has typically been associated with low autologous NAb titers.

### **Clostridium Difficile In A HIV-Infected Cohort: Incidence, Risk Factors, and Clinical Outcomes**

Haines CF, Moore RD, Bartlett JG, Sears CL, Cosgrove SE, Carroll K, Gebo KA. AIDS. 2013; 27(17): 2799-2807.

*Clostridium difficile* is the most commonly reported infectious diarrhea in HIV-infected patients in the United States. The authors set out to determine the incidence, risk factors and clinical presentation of *C. difficile* infections (CDIs) in a cohort of HIV-infected individuals. They performed a nested, case-control analysis with four non-CDI controls randomly selected for each case. They assessed the incidence of CDI in the Johns Hopkins HIV Clinical Cohort between 1 July 2003 and 31 December 2010. Incident cases were defined as first positive *C. difficile* cytotoxin assay or PCR for toxin B gene. They used conditional logistic regression models to assess risk factors for CDI. They abstracted data on the clinical presentation and outcomes from case chart review. They identified 154 incident CDI cases for an incidence of 8.3 cases per 1000 patient years. No unique clinical features of HIV-associated CDI were identified. In multivariate analysis, risk of CDI was independently increased for CD4 cell count of 50 cells/ $\mu$ l or less [adjusted odds ratio (AOR) 20.7, 95% confidence interval (CI) 2.8-151.4], hospital onset CDI (AOR 26.7, 95% CI 3.1-231.2) and use of clindamycin (AOR 27.6, 95% CI 2.2-339.4), fluoroquinolones (AOR 4.5, 95% CI 1.2-17.5), macrolides (AOR 6.3, 95% CI 1.8-22.1), gastric acid suppressants (AOR 3.1, 95% CI 1.4-6.9) or immunosuppressive agents (AOR 6.8, 95% CI 1.2-39.6). The incidence of CDI in HIV-infected patients was twice that previously reported. These data show that compromised cellular immunity, as defined by CD4 cell count of 50 cells/ $\mu$ l or less, is a risk factor for CDI. Clinicians should be aware of the increased CDI risk, particularly in those with severe CD4 cell count suppression.

**Navigating the Risk Environment: Structural Vulnerability, Sex, and Reciprocity Among Women Who Use Methamphetamine** McKenna SA. Int J Drug Policy. 2014; 25(1): 112-115.

Drug users' risk sexual practices contribute to their increased risk for contracting HIV and other sexually transmitted infections. Use of methamphetamine has been associated with a number of high-risk sexual practices such as frequent sexual contacts, multiple sex partners, unprotected sex, and exchange sex. The media construct women who use methamphetamine as engaging in exchange sex to support their drug habit. Despite an abundance of data on exchange sex among heroin and crack users that suggest the importance of examining these practices in context, they remain understudied among female methamphetamine users. This article draws on ongoing ethnographic research with female methamphetamine users. The research participants' risk environment(s) contribute to their structural vulnerability and shape behavior in ways that are sometimes deemed transactional and risky by research, public health, or harm reduction professionals. Understanding the embeddedness of sexual practices in structural context and networks of reciprocity is essential to understanding implications for policy and harm reduction.

**Childhood Economic Strains In Predicting Substance Use In Emerging Adulthood: Mediation Effects Of Youth Self-Control and Parenting Practices** Lee C-T, McClernon FJ, Kollins SH, Prybol K, Fuemmeler BF. J Pediatr Psychol. 2013; 38(10): 1130-1143.

The objective of this study was to examine the influence of childhood economic strains on substance use in young adulthood and to assess the mediating roles of self-control as well as positive parenting during adolescence in a nationally representative longitudinal cohort. The study included data from participants (n = 1,285) in the Panel Study of Income Dynamics, Child Development Supplement, and Transition to Adult. Structural equation modeling was used to evaluate the associations among risk factors during childhood and adolescence that predicted substance use in early adulthood. Conditions of economic strains, especially poverty, during childhood were associated with an increased likelihood of regular smoking in adulthood, which was partially mediated by poorer self-control during adolescence. Self-control is negatively affected by economic strains and serves as a mediator between poverty and risk of regular smoking. Additional research is needed to better understand how economic strains effect the development of self-control.

**A Rapid Gene-Based Genome-Wide Association Test With Multivariate Traits** Basu S, Zhang Y, Ray D, Miller MB, Iacono WG, McGue M. Hum Hered. 2013; 76(2): 53-63.

A gene-based genome-wide association study (GWAS) provides a powerful alternative to the traditional single nucleotide polymorphism (SNP) association analysis due to its substantial reduction in the multiple testing burden and possible gain in power due to modeling multiple SNPs within a gene. A gene-based association analysis on multivariate traits is often of interest, but it imposes substantial analytical as well as computational challenges to implement it at a genome-wide level. The authors propose a rapid implementation of the multivariate multiple linear regression (RMMLR) approach in unrelated individuals as well as in families. Their approach allows for covariates. Moreover, the asymptotic distribution of the test statistic is not heavily influenced by the linkage disequilibrium (LD) among the SNPs and hence can be used efficiently to perform a gene-based GWAS. They have developed a corresponding R package to implement such multivariate gene-based GWAS with this RMMLR approach. Results: Through extensive simulation, we compared several approaches for both single and multivariate traits. The authors' RMMLR approach maintained a correct type I error level even for sets of SNPs in strong LD. It also demonstrated a substantial gain in power to detect a gene when it is associated with a subset of the traits. The authors also studied performances of the approaches on the Minnesota Center for Twin Family Research dataset. Conclusions: In their overall comparison, their RMMLR approach provides an efficient and powerful

tool to perform a gene-based GWAS with single or multivariate traits and maintains the type I error appropriately.

**Incidence and Prevalence Of Intrasubtype HIV-1 Dual Infection In At-Risk Men In The United States** Wagner GA, Pacold ME, Kosakovsky Pond SL, Caballero G, Chaillon A, Rudolph AE, Morris SR, Little SJ, Richman DD, Smith DM. J Infect Dis 2014 Apr; 209(7):1032-1038.

Human immunodeficiency virus type 1 (HIV-1) dual infection (DI) has been associated with decreased CD4 T-cell counts and increased viral loads; however, the frequency of intrasubtype DI is poorly understood. The authors used ultra-deep sequencing (UDS) to estimate the frequency of DI in a primary infection cohort of predominantly men who have sex with men (MSM). HIV-1 genomes from longitudinal blood samples of recently infected, therapy-naïve participants were interrogated with UDS. DI was confirmed when maximum sequence divergence was excessive and supported by phylogenetic analysis. Co-infection was defined as DI at baseline; superinfection was mono infection at baseline and DI at a later time point. Of 118 participants, 7 were co-infected and 10 acquired superinfection. Superinfection incidence rate was 4.96 per 100 person-years (95% confidence interval [CI], 2.67-9.22); 6 occurred in the first year and 4 in the second. Overall cumulative prevalence of intrasubtype B DI was 14.4% (95% CI, 8.6%-22.1%). Primary HIV-1 incidence was 4.37 per 100 person-years (95% CI, 3.56-5.36). Intrasubtype DI was frequent and comparable to primary infection rates among MSM in San Diego; however, superinfection rates declined over time. DI is likely an important component of the HIV epidemic dynamics and development of stronger immune responses to the initial infection may protect from superinfection.

**Real-World Impact Of Neurocognitive Deficits In Acute and Early HIV Infection** Doyle KL, Morgan EE, Morris S, Smith DM, Little S, Iudicello JE, Blackstone K, Moore DJ, Grant I, Letendre SL, Woods SP. J Neurovirol. 2013; 19(6): 565-573.

The acute and early period of HIV-1 infection (AEH) is characterized by neuroinflammatory and immunopathogenic processes that can alter the integrity of neural systems and neurocognitive functions. However, the extent to which central nervous system changes in AEH confer increased risk of real-world functioning (RWF) problems is not known. In the present study, 34 individuals with AEH and 39 seronegative comparison participants completed standardized neuromedical, psychiatric, and neurocognitive research evaluations, alongside a comprehensive assessment of RWF that included cognitive symptoms in daily life, basic and instrumental activities of daily living, clinician-rated global functioning, and employment. Results showed that AEH was associated with a significantly increased risk of dependence in RWF, which was particularly elevated among AEH persons with global neurocognitive impairment (NCI). Among those with AEH, NCI (i.e., deficits in learning and information processing speed), mood disorders (i.e., Bipolar Disorder), and substance dependence (e.g., methamphetamine dependence) were all independently predictive of RWF dependence. Findings suggest that neurocognitively impaired individuals with AEH are at notably elevated risk of clinically significant challenges in normal daily functioning. Screening for neurocognitive, mood, and substance use disorders in AEH may facilitate identification of individuals at high risk of functional dependence who may benefit from psychological and medical strategies to manage their neuropsychiatric conditions.

**An Examination Of The Specificity Of Motivation and Executive Functioning In ADHD Symptom-Clusters In Adolescence** Lopez-Vergara HI, Colder CRJ Pediatr Psychol. 2013; 38(10): 1081-1090.

Motivation and executive functioning are central to the etiology of attention-deficit/hyperactivity disorder (ADHD). Furthermore, it has been hypothesized that motivation should show specificity of



association with ADHD-impulsivity/hyperactivity symptoms, whereas executive functioning should show specificity of association with ADHD-inattention symptoms. This study tests this specificity-hypothesis and extends previous research by conceptualizing motivation to include both reactivity to reward and punishment. Executive functioning was assessed using two different laboratory measures (the Wisconsin-Card-Sort and Stop-Signal Tasks) and motivation was measured using a laboratory measure of sensitivity to reward and punishment (the Point-Scoring-Reaction-Time Task). Findings suggested specificity of association between executive functioning and symptoms of inattention, and between motivation and symptoms of impulsivity/hyperactivity. However, support varied across indices of executive functioning. Results provide support for multiple component models of ADHD symptoms and extend the literature by providing a theoretically based conceptualization of motivation grounded on developmental neuroscience models of motivated behavior.

**Gender and Risk Behaviors For HIV and Sexually Transmitted Infections Among Recently Released Inmates: A Prospective Cohort Study** Binswanger IA, Mueller SR, Beaty BL, Min S-J, Corsi KF. AIDS Care. 2014 Jul; 26(7): 872-881.

Women in prison have a higher prevalence of HIV than men. After release from prison, former inmates have the opportunity to engage in risk behaviors for HIV and other sexually transmitted infections (STIs). The authors sought to assess change in risk behaviors over time and the association of gender with risk behavior in the post release period. In this prospective cohort study, they interviewed 200 former inmates (51 women) approximately two weeks (baseline) and three months (follow-up) after release and tested them for HIV infection at follow-up. They examined the association of gender with unprotected vaginal or anal sex in the last seven days using chi-square and Fisher's exact tests and multivariable logistic regression. At baseline, 22% of men and 41% of women reported unprotected vaginal sex ( $p < 0.01$ ) and 5% of men and 8% of women reported unprotected anal sex ( $p = 0.51$ ). Being younger (OR for each decade increase 0.48, 95% CI = 0.29-0.80), being gay/lesbian or being bisexual (compared with being heterosexual, OR = 4.74, 95% CI = 1.01-22.17 and OR = 3.98, 95% CI = 1.41-11.26, respectively), or reporting a drug of choice of heroin/speedballs or cocaine/crack (compared with marijuana/no drug of choice, OR = 24.00, 95% CI = 5.15-111.81 and OR = 3.49, 95% CI = 1.20-10.18, respectively) was associated with unprotected vaginal or anal sex after adjusting for race, homelessness, and hazardous drinking. At follow-up, 21% of men and 44% of women reported unprotected sex ( $p = 0.005$ ), and female gender (OR = 4.42, 95% CI = 1.79-10.94) and hazardous drinking (compared with not meeting criteria for hazardous drinking, OR = 3.64, 95% CI = 1.34-9.86) were associated with unprotected sex, adjusting for race and homelessness. In this population with a high prevalence of HIV, the authors demonstrated persistent engagement in sexual risk behavior during the post release period. Enhanced efforts to promote sexual health and reduced risk behavior among both male and female current and former prison inmates are needed, including improved access to preventive care and HIV and STI screening, testing, and treatment.

**Achieving A Healthy Zoning Policy In Baltimore: Results Of A Health Impact Assessment Of the Transform Baltimore Zoning Code Rewrite** Johnson Thornton RL, Greiner A, Fichtenberg CM, Feingold BJ, Ellen JM, Jennings JM. Public Health Rep. 2013; 128 Suppl 3: 87-103.

The social determinants of health (SDH) include factors apart from genes and biology that affect population health. Zoning is an urban planning tool that influences neighborhood built environments. The authors describe the methods and results of a health impact assessment (HIA) of a rezoning effort in Baltimore, Maryland, called TransForm Baltimore. The highlight findings specific to physical activity, violent crime, and obesity. They conducted a multistage HIA of TransForm Baltimore using HIA practice guidelines. Key informant interviews identified focus areas for the quantitative assessment. A literature review and a zoning code analysis evaluated potential impacts on

neighborhood factors including physical activity, violent crime, and obesity. They estimated potential impacts in high- and low-poverty neighborhoods. The findings resulted in recommendations to improve the health-promoting potential of TransForm Baltimore. Mixed-use and transit-oriented developments were key goals of TransForm Baltimore. Health impacts identified by stakeholders included walkability and healthy communities. For Baltimore residents, the authors estimated that (1) the percentage of people living in districts allowing mixed-use and off-premise alcohol outlets would nearly triple, (2) 18% would live in transit-oriented development zones, and (3) all residents would live in districts with new lighting and landscaping guidelines. Limiting the concentration of off-premise alcohol outlets represented an opportunity to address health promotion. Changes to Baltimore's zoning code could improve population health including decreasing violent crime. HIAs are an important platform for applying SDH to public health practice. This HIA specifically linked municipal zoning policy with promoting healthier neighborhoods.

**C-Reactive Protein and Substance Use Disorders In Adolescence and Early Adulthood: A Prospective Analysis** Costello EJ, Copeland WE, Shanahan L, Worthman CM, Angold A. Drug Alcohol Depend. 2013; 133(2): 712-717.

Dysregulated immune function and elevated inflammation markers are seen in adults with chronic diseases, including some psychiatric disorders, but evidence on inflammation in the case of drug abuse is conflicting. The objective of this study was to test the concurrent and predictive relations between C-reactive protein (CRP) and use and abuse of alcohol, nicotine and cannabis in a longitudinal, population sample of adolescents and young adults, at the period of highest increase in drug use. Data from the prospective population-based Great Smoky Mountains Study (N=1420) were used, covering children in the community assessed at ages 9-16, 19, and 21. Structured interviews were used to assess substance abuse symptoms and DSM-IV substance use disorders. Bloodspots were collected at each assessment and assayed for CRP. CRP levels were higher in the presence of nicotine, alcohol, and cannabis use and nicotine dependence. In prospective analyses, higher CRP levels predicted cannabis use and nicotine dependence, and nicotine use predicted higher CRP levels, once covariates were included in the models. Significant covariates were age, race (American Indian), and obesity. The inter-relationship of CRP and substance abuse has implications for the later health risks associated with early drug and alcohol use and abuse.

**Online Peer Support For Mental Health Problems In The United States: 2004-2010** DeAndrea DC, Anthony JC. Psychol Med. 2013; 43(11): 2277-2288.

Help seeking for online peer and other social support in response to depression and other mental health problems offers an electronic technology alternative to traditional mental health care. Here, with nationally representative samples of adult community residents in the USA, the authors study online peer support help seeking, estimate its occurrence, and investigate depression and other suspected predictors and correlates, some of which might prove to be causal influences. The data are from nationally representative probability sample surveys of the non-institutionalized US adult population, with a new independent sample assessed via confidential computerized self-assessment modules each year from 2004 to 2010, yielding estimates about online peer support. A total of 264,431 adults participated in these years. An estimated three per 1000 adults (0.3%) seek online peer support for mental health problems each year (95% confidence interval 0.0022-0.0036). Individuals with depression and/or serious psychological distress are strongly over-represented among these adult online peer support help seekers (odds ratio >7,  $p < 0.001$ ). Associations with college education, being non-Hispanic white, being female, and age are also noteworthy ( $p < 0.05$ ). Online help seeking for mental health social support is becoming frequent enough for study in large sample national surveys, and might well be fostered by active neuropsychiatric ailments such as depression or other serious

psychological distress. Open questions remain about whether the result is beneficial, or conditions required for efficacious online peer support, as might be disclosed in definitive evidence from randomized controlled trials.

**DSM-5 Cannabis Use Disorder: A Phenotypic and Genomic Perspective** Agrawal A, Lynskey MT, Bucholz KK, Kapoor M, Almasy L, Dick DM, Edenberg HJ, Foroud T, Goate A, Hancock DB, Hartz S, Johnson EO, Hesselbrock V, Kramer JR, Kuperman S, Nurnberger Jr, JI, Schuckit M, Bierut LJ *Drug Alcohol Depend.* 2014; 134: 362-369.

The authors explore the factor structure of DSM-5 cannabis use disorders; examine its prevalence across European- and African-American respondents as well as its genetic underpinnings, utilizing data from a genome-wide study of single nucleotide polymorphisms (SNPs). They also estimate the heritability of DSM-5 cannabis use disorders explained by these common SNPs. Data on 3053 subjects reporting a lifetime history of cannabis use were utilized. Exploratory and confirmatory factor analyses were conducted to create a factor score, which was used in a genome-wide association analysis. P-values from the single SNP analysis were examined for evidence of gene-based association. The aggregate effect of all SNPs was also estimated using Genome-Wide Complex Traits Analysis. The unidimensionality of DSM-5 cannabis use disorder criteria was demonstrated. Comparing DSM-IV to DSM-5, a decrease in prevalence of cannabis use disorders was only noted in European-American respondents and was exceedingly modest. For the DSM-5 cannabis use disorders factor score, no SNP surpassed the genome-wide significance testing threshold. However, in the European-American subsample, gene-based association testing resulted in significant associations in 3 genes (C17orf58, BPTF and PPM1D) on chromosome 17q24. In aggregate, 21% of the variance in DSM-5 cannabis use disorders was explained by the genome-wide SNPs; however, this estimate was not statistically significant. DSM-5 cannabis use disorder represents a unidimensional construct, the prevalence of which is only modestly elevated above the DSM-IV version. Considerably larger sample sizes will be required to identify individual SNPs associated with cannabis use disorders and unequivocally establish its polygenic underpinnings.

**The Association Of Alcohol Intake With Gamma-Glutamyl Transferase (GGT) Levels: Evidence For Correlated Genetic Effects** van Beek JHDA, de Moor MHM, Geels LM, Sinke M T, de Geus Eco JC, Lubke Gitta H, Kluft C, Neuteboom J, Vink JM, Willemsen G, Boomsma DI. *Drug Alcohol Depend.* 2014; 134: 99-105.

Blood levels of gamma-glutamyl transferase (GGT) are used as a marker for (heavy) alcohol use. The role of GGT in the anti-oxidant defense mechanism that is part of normal metabolism supposes a causal effect of alcohol intake on GGT. However, there is variability in the response of GGT to alcohol use, which may result from genetic differences between individuals. This study aimed to determine whether the epidemiological association between alcohol intake and GGT at the population level is necessarily a causal one or may also reflect effects of genetic pleiotropy (genes influencing multiple traits). Data on alcohol intake (grams alcohol/day) and GGT, originating from twins, their siblings and parents (N=6465) were analyzed with structural equation models. Bivariate genetic models tested whether genetic and environmental factors influencing alcohol intake and GGT correlated significantly. Significant genetic and environmental correlations are consistent with a causal model. If only the genetic correlation is significant, this is evidence for genetic pleiotropy. Phenotypic correlations between alcohol intake and GGT were significant in men ( $r=.17$ ) and women ( $r=.09$ ). The genetic factors underlying alcohol intake correlated significantly with those for GGT, whereas the environmental factors were weakly correlated (explaining 4-7% vs. 1-2% of the variance in GGT respectively). In this healthy population sample, the epidemiological association of alcohol intake with GGT is at least partly explained by genetic pleiotropy. Future longitudinal twin studies should

determine whether a causal mechanism underlying this association might be confined to heavy drinking populations.

**Multivariate Genetic Analyses In Heterogeneous Populations** Lubke G, McArtor D. Behav Genet. 2013 Dec 6 [e-pub ahead of print].

Martin and Eaves (Heredity 38(1):79-95, 1977) proposed a multivariate model for twin and family data in order to investigate potential differences in the genetic and environmental architecture of multivariate phenotypes. The general form of the model is the independent pathway model, which differentiates between genetic and environmental influences at the item level, and therefore permits the decomposition to differ across items. A restricted version is the common pathway model, where the decomposition takes place at the factor level. The paper has spurred numerous studies, and evidence for differences in genetic and environmental architecture has been established for personality and several other psychiatric phenotypes by showing a better fit of the independent pathway model compared to the common pathway model. The authors show that genome-wide association studies (GWAS) that use an aggregate score computed from multiple questionnaire items as a univariate phenotype implicitly assume a similar structure as the common pathway model. It has been shown that in case of a differential genetic and environmental architecture, multivariate GWAS methods can outperform the univariate GWAS approach. However, current multivariate methods rely on the assumptions of phenotypic and genetic homogeneity, that is, item responses are assumed to have the same means and covariance, and genetic effects are assumed to be the same for all subjects. The authors describe a distance-based regression technique that is designed to account for subgroups in the population, and that therefore can account for differential genetic effects. A first evaluation with simulated data shows a substantial increase of power compared to univariate GWAS.

**Variants In HAVCR1 Gene Region Contribute To Hepatitis C Persistence In African Americans**

Wojcik G, Latanich R, Mosbrugger T, Astemborski J, Kirk GD, Mehta SH, Goedert JJ, Kim AY, Seaberg EC, Busch M, Thomas DL, Duggal P, Thio CL. J Infect Dis. 2014; 209(3): 355-359. To confirm previously identified polymorphisms in HAVCR1 that were associated with persistent hepatitis C virus (HCV) infection in individuals of African and of European descent, the authors studied 165 subjects of African descent and 635 subjects of European descent. Because the association was only confirmed in subjects of African descent (rs6880859; odds ratio, 2.42;  $P = .01$ ), they then used 379 subjects of African descent (142 with spontaneous HCV clearance) to fine-map HAVCR1. rs111511318 was strongly associated with HCV persistence after adjusting for IL28B and HLA (adjusted  $P = 8.8 \times 10^{-4}$ ), as was one 81-kb haplotype (adjusted  $P = .0006$ ). The HAVCR1 genomic region is an independent genetic determinant of HCV persistence in individuals of African descent.

**Days Out-Of-Role Due To Common Physical and Mental Health Problems: Results From The Sao Paulo Megacity Mental Health Survey, Brazil** Andrade LH, Baptista MC, Alonso J, Petukhova M, Bruffaerts R, Kessler RC, Silveira CM, Siu ER, Wang Y-P, Viana MC. Clinics (São Paulo) 2013; 68(11): 1392-1399.

The objective of this study was to investigate the relative importance of common physical and mental disorders with regard to the number of days out-of-role (DOR; number of days for which a person is completely unable to work or carry out normal activities because of health problems) in a population-based sample of adults in the Sao Paulo Metropolitan Area, Brazil. The Sao Paulo Megacity Mental Health Survey was administered during face-to-face interviews with 2,942 adult household residents. The presence of 8 chronic physical disorders and 3 classes of mental disorders (mood, anxiety, and substance use disorders) was assessed for the previous year along with the number of days in the previous month for which each respondent was completely unable to work or carry out normal daily

activities due to health problems. Using multiple regression analysis, we examined the associations of the disorders and their comorbidities with the number of days out-of-role while controlling for socio-demographic variables. Both individual-level and population-level associations were assessed. A total of 13.1% of the respondents reported 1 or more days out-of-role in the previous month, with an annual median of 41.4 days out-of-role. The disorders considered in this study accounted for 71.7% of all DOR; the disorders that caused the greatest number of DOR at the individual-level were digestive (22.6), mood (19.9), substance use (15.0), chronic pain (16.5), and anxiety (14.0) disorders. The disorders associated with the highest population-attributable DOR were chronic pain (35.2%), mood (16.5%), and anxiety (15.0%) disorders. Because pain, anxiety, and mood disorders have high effects at both the individual and societal levels, targeted interventions to reduce the impairments associated with these disorders have the highest potential to reduce the societal burdens of chronic illness in the Sao Paulo Metropolitan Area.

**Crystal Methamphetamine Initiation Among Street-Involved Youth** Uhlmann S, Debeck K, Simo A, Kerr T, Montaner JSG, Wood E. *Am J Drug Alcohol Abuse*. 2014; 40(1): 31-36.

Although many settings have recently documented a substantial increase in the use of methamphetamine-type stimulants, recent reviews have underscored the dearth of prospective studies that have examined risk factors associated with the initiation of crystal methamphetamine use. The authors' objectives were to examine rates and risk factors for the initiation of crystal methamphetamine use in a cohort of street-involved youth. Street-involved youth in Vancouver, Canada, were enrolled in a prospective cohort known as the At-Risk Youth Study (ARYS). A total of 205 crystal methamphetamine-naïve participants were assessed semi-annually and Cox regression analyses were used to identify factors independently associated with the initiation of crystal methamphetamine use. Among 205 youth prospectively followed from 2005 to 2012, the incidence density of crystal methamphetamine initiation was 12.2 per 100 person years. In Cox regression analyses, initiation of crystal methamphetamine use was independently associated with previous crack cocaine use (adjusted relative hazard [ARH] =2.24 [95% CI: 1.20-4.20]) and recent drug dealing (ARH=1.98 [95% CI: 1.05-3.71]). Those initiating methamphetamine were also more likely to report a recent nonfatal overdose (ARH=3.63 [95% CI: 1.65-7.98]) and to be male (ARH=2.12 [95% CI: 1.06-4.25]). The authors identified high rates of crystal methamphetamine initiation among this population. Males those involved in the drug trade and those who used crack cocaine were more likely to initiate crystal methamphetamine use. Evidence-based strategies to prevent and treat crystal methamphetamine use are urgently needed.

**Crystal Methamphetamine and Initiation Of Injection Drug Use Among Street-Involved Youth In A Canadian Setting** Werb D, Kerr T, Buxton J, Shoveller J, Richardson C, Montaner J, Wood E. *CMAJ*. 2013; 185 (18): 1569-1575.

Although injection drug use is known to result in a range of health-related harms, including transmission of HIV and fatal overdose little is known about the possible role of synthetic drugs in injection initiation. The authors sought to determine the effect of crystal methamphetamine use on risk of injection initiation among street-involved youth in a Canadian setting. They used Cox regression analyses to identify predictors of injection initiation among injection-naïve street-involved youth enrolled in the At-Risk Youth Study, a prospective cohort study of street-involved youth in Vancouver, British Columbia. Data on circumstances of first injection were also obtained. Between October 2005 and November 2010, a total of 395 drug injection-naïve, street-involved youth provided 1434 observations, with 64 (16.2%) participants initiating injection drug use during the follow-up period, for a cumulative incidence of 21.7 (95% confidence interval [CI] 1.7-41.7) per 100 person-years. In multivariable analysis, recent non injection use of crystal methamphetamine was positively associated

with subsequent injection initiation (adjusted hazard ratio 1.93, 95% CI 1.31-2.85). The drug of first injection was most commonly reported as crystal methamphetamine (14/31 [45%]). Non injection use of crystal methamphetamine predicted subsequent injection initiation, and crystal methamphetamine was the most commonly used drug at the time of first injection. Evidence-based strategies to prevent transition to injection drug use among crystal methamphetamine users are urgently needed.

**Income Level and Drug Related Harm Among People Who Use Injection Drugs In A Canadian Setting** Long C, Debeck K, Feng C, Montaner J, Wood E, Kerr T. Int J Drug Policy. 2013 Dec 1 [e-pub ahead of print].

Higher income is generally associated with better health outcomes; however, among people who inject drugs (IDU) income generation frequently involves activities, such as sex work and drug dealing, which pose significant health risks. Therefore, the authors sought to examine the relationship between level of income and specific drug use patterns and related health risks. This study involved IDU participating in a prospective cohort study in Vancouver, Canada. Monthly income was categorized based on non-fixed quartiles at each follow-up with the lowest level serving as the reference category in generalized linear mixed-effects regression. Among our sample of 1032 IDU, the median average monthly income over the study follow-up was \$1050 [interquartile range=785-2000]. In multivariate analysis, the highest income category was significantly associated with sex work (adjusted odds ratio [AOR]=7.65), drug dealing (AOR=5.06), daily heroin injection (AOR=2.97), daily cocaine injection (AOR=1.65), daily crack smoking (AOR=2.48), binge drug use (AOR=1.57) and unstable housing (AOR=1.67). The high income category was negatively associated with being female (AOR=0.61) and accessing addiction treatment (AOR=0.64), (all  $p < 0.05$ ). In addition, higher income was strongly associated with higher monthly expenditure on drugs (>\$400) (OR=97.8). Among IDU in Vancouver, average monthly income levels were low and higher total monthly income was linked to high-risk income generation strategies as well as a range of drug use patterns characteristic of higher intensity addiction and HIV risk. These findings underscore the need for interventions that provide economic empowerment and address high intensity addiction, especially for female IDU.

**Phenomenology Of Borderline Personality Disorder: The Role Of Race And Socioeconomic Status** De Genna NM, Feske U. J Nerv Ment Dis. 2013; 201(12): 1027-1034.

Little is known about racial differences in borderline personality disorder (BPD) that may influence etiology, phenomenology, and treatment of women with BPD. A total of 83 women with BPD participated in this cross-sectional study:  $n = 41$  white and  $n = 42$  African-American women. Structured interviews were used to assess Axis I and II disorders, and a series of interviews and questionnaires captured internalizing and externalizing symptoms. The white women with BPD reported more severe internalizing symptoms, whereas the African-American women reported more severe externalizing symptoms. Except for the association between race and number of suicide attempts, the relationship between race and internalizing/externalizing symptoms was mediated by socioeconomic status. In conclusion, African-American women with BPD may present with more severe symptoms of lack of anger control and fewer suicidal behaviors than those of white women with BPD, raising the possibility that they are misdiagnosed and receive treatments that are not optimal for BPD.

**HIV Diversity As A Biomarker For HIV Incidence Estimation: Including A High-Resolution Melting Diversity Assay In A Multiassay Algorithm** Cousins MM, Konikoff J, Laeyendecker O, Celum C, Buchbinder SP, Seage 3rd, GR, Kirk GD, Moore RD, Mehta SH, Margolick JB, Brown J, Mayer KH, Koblin BA, Wheeler D, Justman JE, Hodder SL, Quinn TC, Brookmeyer R, Eshleman, SH. J Clin Microbiol. 2014; 52(1): 115-121.

Multiassay algorithms (MAAs) can be used to estimate cross-sectional HIV incidence. The authors previously identified a robust MAA that includes the BED capture enzyme immunoassay (BED-CEIA), the Bio-Rad Avidity assay, viral load, and CD4 cell count. In this report, they evaluated MAAs that includes a high-resolution melting (HRM) diversity assay that does not require sequencing. HRM scores were determined for eight regions of the HIV genome (2 in gag, 1 in pol, and 5 in env). The MAAs that were evaluated included the BED-CEIA, the Bio-Rad Avidity assay, viral load, and the HRM diversity assay, using HRM scores from different regions and a range of region-specific HRM diversity assay cutoffs. The performance characteristics based on the proportion of samples that were classified as MAA positive by duration of infection were determined for each MAA, including the mean window period. The cross-sectional incidence estimates obtained using optimized MAAs were compared to longitudinal incidence estimates for three cohorts in the United States. The performance of the HRM-based MAA was nearly identical to that of the MAA that included CD4 cell count. The HRM-based MAA had a mean window period of 154 days and provided cross-sectional incidence estimates that were similar to those based on cohort follow-up. HIV diversity is a useful biomarker for estimating HIV incidence. MAAs that includes the HRM diversity assay can provide accurate HIV incidence estimates using stored blood plasma or serum samples without a requirement for CD4 cell count data.

**Revisiting the Role Of The Urban Environment In Substance Use: The Case Of Analgesic Overdose Fatalities**

Cerda M, Ransome Y, Keyes KM, Koenen KC, Tardiff K, Vlahov D, Galea S. Am J Public Health. 2013; 103(12): 2252-2260.

The authors examined whether neighborhood social characteristics (income distribution and family fragmentation) and physical characteristics (clean sidewalks and dilapidated housing) were associated with the risk of fatalities caused by analgesic overdose. In a case-control study, they compared 447 unintentional analgesic opioid overdose fatalities (cases) with 3436 unintentional non overdose fatalities and 2530 heroin overdose fatalities (controls) occurring in 59 New York City neighborhoods between 2000 and 2006. Analgesic overdose fatalities were less likely than non-overdose unintentional fatalities to have occurred in higher-income neighborhoods (odds ratio [OR]=0.82; 95% confidence interval [CI]=0.70, 0.96) and more likely to have occurred in fragmented neighborhoods (OR=1.35; 95% CI=1.05, 1.72). They were more likely than heroin overdose fatalities to have occurred in higher-income (OR=1.31; 95% CI=1.12, 1.54) and less fragmented (OR=0.71; 95% CI=0.55, 0.92) neighborhoods. Analgesic overdose fatalities exhibit spatial patterns that are distinct from those of heroin and non-overdose unintentional fatalities. Whereas analgesic fatalities typically occur in lower-income, more fragmented neighborhoods than non-overdose fatalities, they tend to occur in higher-income, less unequal, and less fragmented neighborhoods than heroin fatalities.

**Psychological Dysregulation During Adolescence Mediates the Association Of Parent-Child Attachment In Childhood and Substance Use Disorder In Adulthood**

Zhai ZW, Kirisci L, Tarter RE, Ridenour TA. Am J Drug Alcohol Abuse. 2014; 40(1): 67-74.

This prospective study tested the hypothesis that psychological dysregulation in mid-adolescence (age 16) mediates the association between parent-child attachment in late childhood (age 10-12) and development of substance use disorder (SUD) in adulthood (age 22). The Youth Attachment to Parents Scale (YAPS) was developed in 10-12-year-old boys and girls (N=694) at baseline residing in western Pennsylvania. Psychological dysregulation was measured by the neurobehavioral disinhibition trait. Substance use was assessed at ages 10-12, 12-14, 16 and 19. SUD was diagnosed at age 22 using the Structured Clinical Interview for DSM Disorders. The mediation of parent-child attachment and SUD by neurobehavioral disinhibition was tested separately for mothers and fathers while controlling for baseline substance use. Psychological dysregulation mediates the association between attachment to

mothers and SUD, and partially mediates the association between attachment to fathers and SUD. Significant mediation effects remain after controlling for baseline substance use. Optimal prevention of SUD should include ameliorating both psychological dysregulation predisposing to SUD and quality of the parent-child relationship.

**Longitudinal Patterns Of Anxiety From Childhood To Adulthood: The Great Smoky Mountains Study** Copeland WE, Angold A, Shanahan L, Costello EJ. J Am Acad Child Adolesc Psychiatry. 2014; 53(1): 21-33.

The aims of this study were 2-fold: to provide a brief introduction to the prospective longitudinal Great Smoky Mountains Study and review recent findings; and to use this sample to conduct an epidemiologic analysis of common childhood anxiety disorders. The population-based Great Smoky Mountains Study assessed 1,420 participants from 11 counties in the southeastern United States up to 11 times between ages 9 and 26 years with the structured Child and Adolescent Psychiatric Assessment and its upward extension, the Young Adult Psychiatric Assessment. The U-shaped age prevalence curve for any anxiety disorder was the product of high levels of childhood separation anxiety and adult panic, agoraphobia, and generalized anxiety. More than 1 in 5 subjects met criteria for an anxiety disorder by early adulthood. In terms of cumulative comorbidity, there was evidence of overlap between anxiety disorders, but the level of overlap was generally consistent with what is seen among other common childhood disorders. All childhood anxiety disorders were associated with adverse functioning in at least 1 young adult functional domain, with the poorest outcomes for childhood generalized anxiety and DSM-III-R overanxious disorder. Clinically significant anxiety is a common mental health problem to have had by adulthood. There was little evidence to support the consolidation of anxiety disorders, and some evidence to justify reintroduction of DSM-III-R overanxious disorder. The transition to young adulthood appears to be a key period for understanding the development of common adult anxiety disorders such as panic and agoraphobia.

**Community HIV-1 Drug Resistance Is Associated With Transmitted Drug Resistance** Tilghman MW, Perez-Santiago J, Osorio G, Little SJ, Richman DD, Mathews WC, Haubrich RH, Smith DM. HIV Med. 2014 Jan 12 [e-pub ahead of print].

As community viral load (CVL) measurements are associated with the incidence of new HIV-1 infections in a population, the authors hypothesized that similarly measured community drug resistance (CDR) could predict the prevalence of transmitted drug resistance (TDR). Between 2001 and 2011, the prevalence's of HIV-1 drug resistance for patients with established infection receiving HIV care (i.e., CDR) and TDR in recently infected patients were determined in San Diego. At each position in HIV-1 reverse transcriptase (RT) and protease (pro), drug resistance was evaluated both as the overall prevalence of resistance-associated mutations and by weighting each resistance position to the concurrent viral load of the patient and its proportion to the total viral load of the clinic (CVL). The weighting was the proportion of the CVL associated with patients identified with resistance at each residue. Spearman ranked correlation coefficients were used to determine associations between CDR and TDR. The authors analyzed 1088 resistance tests for 971 clinic patients and baseline resistance tests for 542 recently infected patients. CDR at positions 30, 46, and 88 in pro was associated with TDR between 2001 and 2011. When CDR was weighted by the viral load of patients, CDR was associated with TDR at position 103 in RT. Each of these associations was corroborated at least once using shorter measurement intervals. Despite evaluation of a limited percentage of chronically infected patients in San Diego, CDR correlated with TDR at key resistance positions and therefore may be a useful tool with which to predict the prevalence of TDR.



**Interaction Matters: Quantifying Conduct Problem Depressive Symptoms Interaction and Its Association With Adolescent Alcohol, Cigarette, and Marijuana Use In A National Sample**

Maslow J, Schulenberg JE. Dev Psychopathol. 2013; 25(4 Pt 1): 1029-1043.

Substance use is a major contributor to morbidity and mortality among American adolescents. Conduct problems and depressive symptoms have each been found to be associated with adolescent substance use. Although they are highly comorbid, the role of the interaction of conduct problems and depressive symptoms in substance use is not clear. In national samples of 8th-, 10th-, and 12th-grade students from the Monitoring the Future study, latent moderated structural equation modeling was used to estimate the association of conduct problems, depressive symptoms, and their interaction to the use of alcohol (including binge drinking), cigarettes, and marijuana. Moderation by age and sex was tested. The interaction of conduct problems with depressive symptoms was a strong predictor of substance use, particularly among younger adolescents. With few exceptions, adolescents with high levels of both conduct problems and depressive symptoms used substances most frequently. Conduct problems were a strong positive predictor of substance use, and depressive symptoms were a weak positive predictor. Whereas conduct problems are often thought to be a primary predictor of substance use, this study revealed that depressive symptoms potentiate the relation of conduct problems to substance use. Therefore, substance use prevention efforts should target both depressive symptoms and conduct problems.

**Structural Bridging Network Position Is Associated With HIV Status In A Younger Black Men Who Have Sex With Men Epidemic**

Shah NS, Iveniuk J, Muth SQ, Michaels S, Jose J-A, Laumann EO, Schneider JA. AIDS Behav. 2014; 18(2): 335-345.

Younger Black men who have sex with men (BMSM) ages 16-29 have the highest rates of HIV in the United States. Despite increased attention to social and sexual networks as a framework for biomedical intervention, the role of measured network positions, such as bridging and their relationship to HIV risk has received limited attention. A network sample (N = 620) of BMSM respondents (N = 154) and their MSM and transgendered person network members (N = 466) was generated through respondent driven sampling of BMSM and elicitation of their personal networks. Bridging status of each network member was determined by a constraint measure and was used to assess the relationship between this bridging and unprotected anal intercourse (UAI), sex-drug use (SDU), group sex (GS) and HIV status within the network in South Chicago. Low, moderate and high bridging was observed in 411 (66.8 %), 81 (13.2 %) and 123 (20.0 %) of the network. In addition to age and having sex with men only, moderate and high levels of bridging were associated with HIV status (aOR 3.19; 95 % CI 1.58-6.45 and aOR 3.83; 95 % CI 1.23-11.95, respectively). Risk behaviors observed including UAS, GS, and SDU were not associated with HIV status, however, they clustered together in their associations with one another. Bridging network position but not risk behavior was associated with HIV status in this network sample of younger BMSM. Socio-structural features such as position within the network may be important when implementing effective HIV prevention interventions in younger BMSM populations.

**Emergence Of Cocaine and Methamphetamine Injection Among HIV-Positive Injection Drug Users In Northern and Western India**

Shah NS, Iveniuk J, Muth SQ, Michaels S, Jose J-A, Laumann EO, Schneider JA. AIDS Behav. 2014; 18(2): 335-345.

Little is known regarding the epidemiology of drug injection and risk behaviors among injection drug users (IDUs) across India. In particular, there is limited data on the prevalence of stimulant injection. The authors sampled 801 HIV positive IDUs from 14 locations throughout India to represent the geography of India as well as the diversity in IDU epidemic stage (established epidemics, emerging epidemics and large cities). All participants underwent a behavioral survey and blood draw. Given

prior associations with stimulant injection and HIV risk, we compared stimulant injectors (cocaine and/or methamphetamine) to those who injected opiates and/or pharmaceuticals only. The median age was 33; 86% were male. The primary drugs injected were heroin, buprenorphine and other pharmaceuticals. In all but four sites, >50% of those actively injecting reported needle sharing. Stimulant injection was most common in emerging epidemics. Compared to exclusive opiate injectors, stimulant injectors were significantly younger, more likely to be educated and employed, more likely to report non-injection use of heroin, crack/cocaine and amphetamines, heavy alcohol use, recent needle sharing (71% vs. 57%), sex with a casual partner (57% vs. 31%) and men having sex with other men (33% vs. 9%;  $p<0.01$  for all). Emerging IDU epidemics have a drug/sexual risk profile not previously been observed in India. Given the high prevalence of stimulant injection in these populations, HIV prevention/treatment programs may need to be redesigned to maximize effectiveness. The high levels of injection sharing overall reinforce the need to ensure access to harm-reduction services for all. Mehta SH, Srikrishnan AK, Noble E, Vasudevan CK, Solomon S, Kumar MS, Solomo SS. *Drug Alcohol Depend.* 2014; 135: 160-165.

**A Simulative Comparison Of Respondent Driven Sampling With Incentivized Snowball Sampling - The "Strudel Effect"** Gyarmathy VA, Johnston LG, Caplinskiene I, Caplinskas S, Latkin C. *Drug Alcohol Depend.* 2014; 135: 71-77.

Respondent driven sampling (RDS) and incentivized snowball sampling (ISS) are two sampling methods that are commonly used to reach people who inject drugs (PWID). The authors generated a set of simulated RDS samples on an actual sociometric ISS sample of PWID in Vilnius, Lithuania ("original sample") to assess if the simulated RDS estimates were statistically significantly different from the original ISS sample prevalence's for HIV (9.8%), Hepatitis A (43.6%), Hepatitis B (Anti-HBc 43.9% and HBsAg 3.4%), Hepatitis C (87.5%), syphilis (6.8%) and Chlamydia (8.8%) infections and for selected behavioral risk characteristics. The original sample consisted of a large component of 249 people (83% of the sample) and 13 smaller components with 1-12 individuals. Generally, as long as all seeds were recruited from the large component of the original sample, the simulation samples simply recreated the large component. There were no significant differences between the large component and the entire original sample for the characteristics of interest. Altogether 99.2% of 360 simulation sample point estimates was within the confidence interval of the original prevalence values for the characteristics of interest. When population characteristics are reflected in large network components that dominate the population, RDS and ISS may produce samples that have statistically non-different prevalence values, even though some isolated network components may be under-sampled and/or statistically significantly different from the main groups. This so-called "strudel effect" is discussed in the paper.

**Health Correlates Of Co-Occurring Substance Use For Women With HIV In Cocaine Use Recovery** McCabe BE, Feaster DJ, Mitrani VB. *Addict Behav.* 2014; 39(3): 725-728.

The goal of this study was to examine clinical correlates of alcohol, opioid, cannabis, sedative, or other co-occurring substance use disorders in a sample of 124 HIV+ women in recovery from cocaine use disorders. Data was collected from a baseline assessment for a randomized trial comparing a family therapy intervention to a health promotion group intervention. Substance use disorders were assessed with a computer-administered structured diagnostic interview. Psychological distress was measured with the Brief Symptom Inventory. Sleep problems were measured with the Short Sleep Index from the Hamilton Anxiety and Depression Rating Scales. Pain was assessed with items from the Medical Outcomes Study-HIV scale. HIV health was assessed with blood tests for T-cell count and HIV Viral Load Suppression, as well as a nurse-administered symptom assessment. Women with a co-occurring opioid use disorder were significantly more likely to have psychological distress and sleep problems,

but less likely to have severe pain. Even though there was no difference in T-cell count or Viral Load, women with opioid use disorder were significantly more likely to have high HIV symptoms. Women in recovery with HIV who have co-occurring cocaine use and opioid use disorders were more likely to have several indicators of worse mental and physical health. Interventions may need to be tailored to meet the needs of this subgroup of women. Future research should examine whether these co-occurring conditions are associated with greater likelihood of relapse or poor treatment response, and whether this higher-risk profile exists in other groups.

**Estimating the Number Of Young Black Men Who Have Sex With Men (YBMSM) On the South Side Of Chicago: Towards HIV Elimination Within US Urban Communities** Livak B, Michaels S, Green K, Nelson C, Westbrook M, Simpson Y, Prachand NG, Benbow N, Schneider JA. J Urban Health. 2013; 90(6): 1205-1213.

The rate of HIV infection among young Black men who have sex with men (YBMSM) aged 16-29 is increasing significantly in the United States. Prevention in this population would considerably impact future health-care resources given the need for lifelong antiretroviral. An YBMSM population estimate is needed to assist HIV prevention program planning. This analysis estimates the number of YBMSM aged 16-29 living on the south side of Chicago (SSC), the Chicago HIV epicenter, as the first step in eliminating HIV in this population. Three methods were utilized to estimate the number of YBMSM in the SSC. First, an indirect approach following the formula  $a=k/b$ ; where  $a$  = the estimated number of YBMSM,  $k$  = the average YBMSM HIV prevalence estimate, and  $b$ =the YBMSM population-based HIV seropositivity rate. Second, data from the most recent National Survey of Family Growth (NSFG) was used to estimate the proportion of Black men who report having sex with a man. Third, a modified Delphi approach was used, which averaged community expert estimates. The indirect approach yielded an average estimate of 11.7 % YBMSM, the NSFG yielded a 4.2 % (95 % CI 2.28-6.21) estimate, and the modified Delphi approach yielded estimates of 3.0 % (2.3-3.6), 16.8 % (14.5-19.1), and 25 % (22.0-27.0); an average of 14.9 %. The crude average of the three methods was 10.2 %. Applied to SSC, this results to 5,578 YBMSM. The estimate of 5,578 YBMSM represents a group that can be feasibly reached with HIV prevention efforts. Population estimates of those most at risk for HIV will help public health officials allocate resources, offering potential for elimination of new HIV cases.

**Initial Reactions To Tobacco and Cannabis Smoking: A Twin Study** Agrawal A, Madden PAF, Bucholz KK, Heath AC, Lynskey MT. Addiction. 2014 April; 109(4): 663-671.

Initial subjective reactions to cannabis and tobacco, broadly classified as positive or negative; have previously been explored for their associations with onset and maintenance of subsequent abuse/dependence. The authors examine (i) the factorial architecture of self-reported initial reactions to cannabis and tobacco; (ii) whether these factors associate with concurrently reported age at onset of DSM-IV diagnosis of nicotine dependence and cannabis abuse/dependence; and (iii) estimate heritable variation in and co-variation between the factors. Factorial and exploratory structural equation modeling was conducted to examine the factor structure of initial reactions. Cox proportional hazards modeling was employed to examine their association with time to onset of diagnosis of DSM-IV nicotine dependence and cannabis abuse/dependence. Classical twin modeling, using univariate and multivariate models, was used to parse variance in each factor (and the covariance between factors) to their additive genetic, shared environmental and non-shared environmental sources. General population sample of Caucasian female twins aged 18-32 years, with a life-time history of tobacco [n=2393] and cannabis [n=1445] use. Self-report of initial subjective reactions to tobacco (cigarettes) and cannabis the first time they were used and time to onset of life-time history of DSM-IV diagnosis of abuse (cannabis) and dependence (cannabis or nicotine). Factors representing putatively positive and negative reactions to cannabis and tobacco emerged. Initial reactions to tobacco were associated with

onset of DSM-IV diagnosis of nicotine dependence and cannabis abuse/dependence while initial reactions to cannabis were associated with onset of DSM-IV diagnosis of cannabis abuse/dependence alone. Genetic factors played a moderate role in each factor (heritability of 27-35%,  $P < 0.05$ ), with the remaining variance attributed to individual-specific environment. Co-variation across the factors indexing positive and negative initial reactions was attributable to genetic sources (0.18-0.58,  $P < 0.05$ ) and to overlapping individual-specific environmental factors (-0.16 to 0.36,  $P < 0.05$ ). Initial subjective reactions to tobacco are associated with onset of DSM-IV diagnosis of nicotine dependence and cannabis abuse/dependence while initial subjective reactions to cannabis are only associated with onset of diagnosis of DSM-IV cannabis abuse/dependence. Genetic and environmental factors underpin the overlap across the factors representing initial reactions, both positive and negative.

**White and Black Adolescent Females Differ In Profiles and Longitudinal Patterns Of Alcohol, Cigarette, And Marijuana Use** Chung T, Kim KH, Hipwell AE, Stepp SD. Psychol Addict Behav. 2013; 27(4): 1110-1121.

Emerging research suggests that white youth are more likely to show continuity of alcohol use in the year after drinking onset, compared with black youth. Little is known, however, regarding racial differences in year-to-year continuity of alcohol, cigarette, and marijuana use during adolescence, particularly among females, who are at greater risk for certain substance-related harm than males. This study used latent class/transition analysis to identify profiles of past year alcohol, cigarette, and marijuana use at ages 13-17 in a community sample of 1076 adolescent females (57% black, 43% white). Three profiles of past year substance uses were identified in separate analyses by race: "no use," "alcohol only" and "polydrug use." Although similar labels describe the profiles, the probability of endorsing use of a particular substance for a given profile differed by race, precluding direct comparison. Latent transition analyses of five annual waves covering ages 13-17 indicated that an intermittent pattern of use (e.g., use in one year, but not the next) was relatively low at all ages among white girls, but among black girls, an intermittent pattern of use began to decline at age 15. Among black girls, conduct problems at age 12 predicted substance using profiles at age 13, whereas among white girls, intentions to use alcohol and cigarettes at age 12 predicted substance using profiles at age 13. Racial differences in girls' substance use profiles suggest the potential utility of culturally tailored interventions that focus on differences in risk for specific substances and relatively distinct early patterns of use.

**Reciprocal Associations Between PTSD Symptoms And Alcohol Involvement In College: A Three-Year Trait-State-Error Analysis** Read JP, Waddell JD, Colder CR. J Abnorm Psychol. 2013; 122(4): 984-997.

Bidirectional associations between posttraumatic stress disorder (PTSD) symptoms and alcohol involvement have been theorized, but have not been tested empirically. In this study, the authors examined these relations at the transition into and over the first 3 years of college by using an analytic approach (Trait-State-Error Modeling [TSE]; Kenny & Zautra, 1995) that allowed us to examine prospective, reciprocal associations among these constructs while accounting for intraindividual stability. Young adults ( $N = 486$ ) were recruited at matriculation into college and assessed by Web survey in September of the first college year (T1) and 11 additional time points over 3 years. Findings showed evidence of prospective associations from alcohol involvement (both use and problems) to PTSD symptoms over the 3-year assessment period. The authors also observed prospective relations from PTSD symptoms to alcohol involvement over time. Patterns of co-variation in trait vulnerability for alcohol involvement and PTSD symptoms differed from crossed-lagged associations among state-like variance in these constructs. Results suggest that PTSD symptoms and alcohol involvement each

predict the other over the course of college. Findings also highlight the importance of considering both time-varying and stable sources of variation in these associations.

**Relational Interventions For Child Maltreatment: Past, Present, and Future Perspectives** Tooth SL, Gravened-Davis JA, Guild DJ, Cochiti D. Dev Psychopathol. 2013; 25(4 Pt 2): 1601-1617.

It is well established that child maltreatment has significant deleterious effects for the individual as well as for society. The authors briefly review research regarding the impact of child maltreatment on the attachment relationship, highlighting the need for relational interventions for maltreated children and their families to effectively thwart negative developmental cascades that are so often observed in the context of child maltreatment. Next, historical and contemporaneous perspectives on relational interventions for individuals with histories of child maltreatment are discussed, with attention to the empirical evidence for and the current evidence-based status of several relationally based interventions for child maltreatment. Differential sensitivity to the environment is then discussed as a theoretical framework with important implications for interventions for individuals who have been reared in maltreating environments. Current research on neurobiology and maltreatment is then reviewed, with an emphasis on the need for future investigations on genetic variants, epigenetics, and the efficacy of relational interventions for maltreated children. The authors conclude with a discussion of the tenets of developmental psychopathology, their implications for relational interventions for child maltreatment, and recommendations for advancing the development, provision, and evaluation of relational interventions for individuals with histories of child maltreatment.

## **PREVENTION RESEARCH**

**Youth Problem Behaviors 8 Years After Implementing the Communities That Care Prevention System: A Community-Randomized Trial** Hawkins JD, Oesterle S, Brown EC, Abbott RD, Catalano RF. JAMA Pediatr. 2014; 168(2): 122-129.

Community-based efforts to prevent adolescent problem behaviors are essential to promote public health and achieve collective impact community wide. The objective of this study was to test whether the Communities That Care (CTC) prevention system reduced levels of risk and adolescent problem behaviors community wide 8 years after implementation of CTC. A community-randomized trial was performed in 24 small towns in 7 states, matched within state, assigned randomly to a control or intervention group in 2003. All fifth-grade students attending public schools in study communities in 2003-2004 who received consent from their parents to participate (76.4% of the eligible population) were included. A panel of 4407 fifth graders was surveyed through 12th grade, with 92.5% of the sample participating at the last follow-up. A coalition of community stakeholders received training and technical assistance to install CTC, used epidemiologic data to identify elevated risk factors and depressed protective factors for adolescent problem behaviors in the community, and implemented tested and effective programs for youths aged 10 to 14 years as well as their families and schools to address their community's elevated risks. Main outcomes and measures obtained included levels of targeted risk; sustained abstinence, and cumulative incidence by grade 12; and current prevalence of tobacco, alcohol, and other drug use, delinquency, and violence in 12th grade. By spring of 12th grade, students in CTC communities were more likely than students in control communities to have abstained from any drug use (adjusted risk ratio [ARR] =1.32; 95% CI, 1.06-1.63), drinking alcohol (ARR=1.31; 95% CI, 1.09-1.58), smoking cigarettes (ARR=1.13; 95% CI, 1.01-1.27), and engaging in delinquency (ARR=1.18; 95% CI, 1.03-1.36). They were also less likely to ever have committed a violent act (ARR=0.86; 95% CI, 0.76-0.98). There were no significant differences by intervention group in targeted risks, the prevalence of past-month or past-year substance use, or past-year delinquency or violence. The authors conclude that using the CTC system continued to prevent the initiation of adolescent problem behaviors through 12th grade, 8 years after implementation of CTC and 3 years after study-provided resources ended, but did not produce reductions in current levels of risk or current prevalence of problem behavior in 12th grade.

**Prevention Effects Ameliorate the Prospective Association Between Nonsupportive Parenting and Diminished Telomere Length** Brody GH, Yu T, Beach SRH. Prevention Science 2014 March 16 [e-pub ahead of print].

Telomere length (TL) is an indicator of general systemic aging, with diminished TL associated with several chronic diseases of aging and with heightened mortality risk. Research has begun to focus on the ways in which stress contributes to telomere attrition. The purposes of this study were (a) to establish whether exposure to nonsupportive parenting, defined as high levels of conflict and rancor with low levels of warmth and emotional support, at age 17 would forecast TL 5 years later; and (b) to determine whether participation in an efficacious family-centered prevention program could ameliorate any associations that emerged. Rural African American adolescents participated in the Adults in the Making (AIM) program or a control condition. Primary caregivers provided data on nonsupportive parenting during a pretest when adolescents were age 17. Adolescents provided data on anger at the pretest and at a posttest administered 7 months later. When the youths were age 22, TL was assayed from a blood draw. The results indicated that heightened nonsupportive parenting forecast diminished TL among young adults in the control condition but not among those who participated in AIM; socioeconomic status risk, life stress, and the use of alcohol and cigarettes at age 17, and blood pressure and body mass index at age 22, were controlled. Subsequent exploratory analyses suggested

that AIM-induced reductions in adolescents' anger served as a mediator connecting group assignment to TL. The results suggest that the cellular-level sequelae of nonsupportive parenting and stress are not immutable.

**Randomized Controlled Trial Of Universal Postnatal Nurse Home Visiting: Impact On Emergency Care**

Dodge KA, Goodman WB, Murphy RA, O'Donnell K, Sato J. Pediatrics. 2013; 132 Suppl 2: S140-146.

Although nurse home visiting has proven efficacious with small samples, scaling up to community populations with diverse families has not yet proven effective. The Durham Connects program was developed in collaboration with community leaders as a brief, universal, postnatal nurse home visiting intervention designed to screen for risk, provide brief intervention, and connect families with more intensive evidence-based services as needed. This study tested program effectiveness in reducing infant emergency medical care between birth and age 12 months. All 4,777 resident births in Durham, North Carolina across 18 months were randomly assigned, with even birth date families to intervention and odd birth date families to control. Intervention families were offered 3 to 7 contacts between 3 and 12 weeks after birth to assess family needs and connect parents with community resources to improve infant health and well-being. Hospital records were analyzed by using an intent-to-treat design to evaluate impact among a representative subset of 549 families. After demographic factors (ie, birth risk, Medicaid status, ethnicity, and single parenthood) were covered, relative to control families, families assigned to intervention had 50% less total emergency medical care use (mean [M] emergency department visits and hospital overnights) ( $M(\text{intervention}) = 0.78$  and  $M(\text{control}) = 1.57$ ;  $P < .001$ , effect size = 0.28) across the first 12 months of life. This brief, universal, postnatal nurse home visiting program improves population-level infant health care outcomes for the first 12 months of life. Nurse home visiting can be implemented universally at high fidelity with positive impacts on infant emergency health care that are similar to those of longer, more intensive home visiting programs. This approach offers a novel solution to the paradox of targeting by offering individually tailored intervention while achieving population-level impact.

**Comparative Effectiveness Of A Faith-Based HIV Intervention For African American Women: Importance Of Enhancing Religious Social Capital**

Wingood GM, Robinson LR, Braxton ND, Er DL, Conner AC, Renfro TL, Rubtsova AA, Hardin JW, Diclemente RJ. Am J Public Health. 2013; 103(12): 2226-2233.

The authors assessed the effectiveness of P4 for Women, a faith-based HIV intervention. They used a 2-arm comparative effectiveness trial involving 134 African American women aged 18 to 34 years to compare the effectiveness of the Centers for Disease Control and Prevention-defined evidence-based Sisters Informing Sisters about Topics on AIDS (SISTA) HIV intervention with P4 for Women, an adapted faith-based version of SISTA. Participants were recruited from a large black church in Atlanta, Georgia, and completed assessments at baseline and follow-up. Both SISTA and P4 for Women had statistically significant effects on this study's primary outcome-consistent condom use in the past 90 days-as well as other sexual behaviors. However, P4 for Women also had statistically significant effects on the number of weeks women were abstinent, on all psychosocial mediators, and most noteworthy, on all measures of religious social capital. Results were achieved by enhancing structural social capital through ministry participation, religious values and norms, linking trust and by reducing negative religious coping. High intervention attendance may indicate the feasibility of conducting faith-based HIV prevention research for African American women. P4 for Women enhanced abstinence and safer sex practices as well as religious social capital, and was more acceptable than SISTA. Such efforts may assist faith leaders in responding to the HIV epidemic in African American women.

**A Randomized Controlled Trial Of the Community-Friendly Health Recovery Program (CHRP) Among High-Risk Drug Users In Treatment** Copenhagen MM, Lee I-C, Baldwin P. AIDS Behav. 2013; 17(9): 2902-2913.

Existing evidence-based HIV risk reduction interventions have not been designed for implementation within clinical settings, such as methadone maintenance programs, where many high-risk drug users seek treatment services. The authors therefore systematically developed an adapted, significantly shortened, version of a comprehensive evidence-based intervention called the Community-friendly Health Recovery Program (CHRP) which has demonstrated preliminary evidence of efficacy in a feasibility/acceptability study already published. In a randomized controlled trial reported here, the authors tested the efficacy of the CHRP intervention among high-risk drug users newly enrolled in drug treatment at an inner-city methadone maintenance program. The CHRP intervention produced improvements in drug risk reduction knowledge as well as demonstrated sex- and drug-risk reduction skills. Support was found for the IMB model of health behavior change. Implications for future intervention research and practice are considered.

**Adolescents' Attitudes Toward Anti Marijuana Ads, Usage Intentions, and Actual Marijuana Usage** Alvaro EM, Crano WD, Siegel JT, Hohman Z, Johnson I, Nakawaki B. Psychol Addict Behav. 2013; 27(4): 1027-1035.

The association of adolescents' appraisals of the anti marijuana TV ads used in the National Youth Antidrug Media Campaign with future marijuana use was investigated. The 12- to 18-year-old respondents (N = 2,993) were first classified as users, resolute nonusers, or vulnerable nonusers (Crano, Siegel, Alvaro, Lac, & Hemovich, 2008). Usage status and the covariates of gender, age, and attitudes toward marijuana were used to predict attitudes toward the ads (Aad) in the first phase of a multilevel linear analysis. All covariates were significantly associated with Aad, as was usage status: Resolute nonusers evaluated the ads significantly more positively than vulnerable nonusers and users (all  $ps < .001$ ), who did not differ. In the second phase, the covariates along with Aad and respondents' usage status predicted intentions and actual usage 1 year after initial measurement. The lagged analysis disclosed negative associations between Aad and usage intentions and between Aad and actual marijuana use (both  $ps < .05$ ); however, this association held only for users ( $p < .01$ ), not vulnerable or resolute nonusers. Users who reported more positive attitudes toward the ads were less likely to report intention to use marijuana and to continue marijuana use at 1-year follow-up. These findings may inform designers of persuasion-based prevention campaigns, guiding pre-implementation efforts in the design of ads that targeted groups find appealing and thus, influential.

**Characteristics Of Men Who Have Sex With Men (MSM) Who Attend Sex Parties: Results From A National Online Sample In the USA** Grov C, Rendina HJ, Breslow AS, Ventuneac A, Adelson S, Parsons JT. Sex Transm Infect. 2014; 90(1): 26-32.

The aim of this study was to compare three groups of men who have sex with men (MSM)-men who had attended a sex party in the past year (45.2%); men who had been to a sex party more than a year ago (23.3%); and men who had never been to one (31.5%)-on socio-demographic and behavioral characteristics. In spring 2012, 2,063 sexually active MSM in the USA were recruited using banner advertising on a sexual networking website to complete an online survey about their sexual behavior and attendance at sex parties. A significantly higher proportion of past year attendees were HIV-positive (28.1%), single (31.7%), demonstrated sexual compulsivity symptomology (39.2%), recently used drugs (67.8%), averaged the greatest number of recent male partners (Mdn=15, <90 days), and had greater instances of recent unprotected anal intercourse (UAI) with male partners (median=3, <90 days). Adjusting for covariates, those having been to a sex party in the last year were significantly more likely than others to report UAI. Free lubricant (93.4%) and condoms (81.0%) were the most



desirable services/products men wanted at sex parties. More than half of men having been to a sex party expressed interest in free rapid HIV testing at sex parties (52.8%); however, few considered it acceptable to see “medical providers” (11.7%) and “peer outreach workers” (9.5%) at sex parties. MSM who have attended a sex party in the last year are appropriate candidates for targeted HIV and sexually transmitted infection (STI) prevention. Collaborating with event promoters presents valuable opportunities to provide condoms, lubricant and HIV/STI testing.

### **The Influence Of Individual, Partner, and Relationship Factors On HIV Testing In Adolescents**

Talib HJ, Silver EJ, Coupey SM, Bauman LJ. AIDS Patient Care STDS. 2013; 27(11): 637-645.

Early identification of HIV by increasing testing is a national priority; however, little is known about HIV testing behaviors in high school age adolescents. The authors examined the association of individual, partner, and relationship factors with HIV testing using a computer-assisted survey administered from 2003 to 2006 in a community sample of 980 sexually active 14- to 17-year-olds (56% female, 55% Latino, 25% African American) living in a jurisdiction with a high AIDS burden. Twenty percent reported their first sexual encounter as having occurred when they were <13 years of age, 33% had had four or more lifetime sexual partners, 21% reported high partner HIV-risk behavior, and 428 (44%) had been tested for HIV. In the authors’ final regression model, independent associations with HIV testing included being female (OR=1.68 [1.23-2.30]), older (OR=1.41 [1.21-1.65]), and having had four or more lifetime sexual partners (OR=2.24 [1.64-3.05]). The strongest independent predictor of HIV testing was having high HIV-related partner communication (OR=3.70 [2.77-4.94]). Being in a serious committed relationship (OR=1.39 [1.02-1.87]) was also independently associated with HIV testing, whereas reporting high worry about HIV/AIDS (OR=0.53 [0.40-0.71]) was independently negatively associated with HIV testing. High HIV/AIDS knowledge, high partner HIV risk behavior, and young age at first sexual encounter were not associated with testing. These findings suggest that, for high school aged adolescents, optimal strategies to promote HIV testing should look beyond increasing HIV/AIDS knowledge and identifying individual risk behaviors to also considering the role of partners and relationships and their influence on testing behavior.

### **Differential Impact Of Cumulative SES Risk On Methylation Of Protein-Protein Interaction Pathways As A Function Of SLC6A4 Genetic Variation In African American Young Adults**

Beach SRH, Dogan MV, Brody GH, Philibert RA. Biol Psychol. 2014; 96: 28-34.

Exposure to cumulative SES risk in childhood may interact with variability at the serotonin transporter linked polymorphic region (5HTTLPR) to alter DNA methylation across interacting sets of proteins. DNA was obtained from 388 African Americans at age 19. Genotype at the 5HTTLPR was determined, and methylation ratios for C-phosphate-G (CpG) residues were assessed. Exposure to cumulative SES risk was determined using repeated parental reports at ages 11-13. At high SES risk, CpG methylation patterns indicated altered cellular stress response in women, but not men, who carried a short allele at the 5HTTLPR. These changes in methylation patterns may lead to increases in mental and physical health risks. No genotype effect emerged for either women or men at low SES risk. Methylation patterns provide guidance in identifying pathways by which genetic susceptibility is transformed into adverse outcomes years later.

### **Factors Associated With Sexual Arousal, Sexual Sensation Seeking and Sexual Satisfaction Among Female African American Adolescents.**

Sales JM, Smearman EL, Brody GH, Milhausen R, Philibert RA, Diclemente RJ. Sex Health. 2013; 10(6): 512-521.

Sexuality-related constructs, such as sexual arousal, sexual sensation seeking (SSS) and sexual satisfaction, have been related to sexual behaviors that place one at risk of adverse consequences, such as sexually transmissible infections, HIV and unintended pregnancy. The bio psychosocial model

posits an array of factors, ranging from social environmental factors to biological and psychological predispositions that may be associated with these sexuality constructs in adolescents. Female African Americans aged 14-20 years were recruited from reproductive health clinics for an HIV intervention. Baseline survey and follow-up DNA data (n=304) were used to assess biological, psychological and social environmental associations with the sexuality constructs of arousal, SSS and sexual satisfaction. Multivariate linear regression analysis revealed that a higher depressive symptom rating was associated with higher arousability, whereas short serotonin transporter gene allele(s) status was associated with lower arousability. Impulsivity and perceived peer norms supportive of unsafe sexual behaviors were associated with increased SSS, whereas short serotonin transporter gene allele(s) status was associated with lower SSS. Higher social support was associated with higher levels of sexual satisfaction, whereas short serotonin transporter gene allele(s) status was associated with lower satisfaction. The sexuality constructs were also significantly related to the number of sex partners, the frequency of vaginal sex and the number of unprotected vaginal sex acts in the past 6 months. The findings emphasize the importance of understanding bio psychosocial factors, including the role of serotonin as an indicator of natural variations in sexual inclination and behaviors, that influence sexuality constructs, which, in turn, are associated with sexual behaviors, to allow further refinement of sexual health clinical services and programs and promote the development of healthy sexuality.

**Parents Of Older At-Risk Youth: A Retention Challenge For Preventive Intervention** Hooven C, Pike K, Walsh E. J Prim Prev. 2013; 34(6): 423-438.

The authors examined data from 162 families who participated in the prevention program Parents and Youth with Schools, which targeted at-risk high school youth and parents, to understand parent retention in the 15-session Parents as Partners program. They obtained reports from youth, parents and parent interventionists, which included both time-invariant and time-varying data regarding demographic factors; parent, youth and family characteristics; and parents' response to intervention. Utilizing event history analysis, the authors examined data sequentially in order to determine those variables that predicted continued parent attendance. In the model examining all areas simultaneously, the predictors of parent retention across the full program were parent minority status and age, teen anger and parent-teen conflict over school attendance, as well as parents' reports of group support and interventionists' report of parents' commitment. Overall, the analyses indicated that participants' characteristics, as well as their measureable response to the intervention, can alert researchers to potential program disengagement. Monitoring indicators of disengagement will help researchers focus resources early in the intervention process in order to maximize parent attendance and increase the success of prevention programs.

**A Randomized Controlled Trial Of A Group Motivational Interviewing Intervention For Adolescents With A First Time Alcohol Or Drug Offense** D'Amico EJ, Hunter SB, Miles JNV, Ewing BA, Osilla KC. J Subst Abuse Treat. 2013; 45(5): 400-408.

Group motivational interviewing (MI) interventions that target youth at-risk for alcohol and other drug (AOD) use may prevent future negative consequences. Youth in a teen court setting [n=193; 67% male, 45% Hispanic; mean age 16.6 (SD=1.05)] were randomized to receive a group MI intervention, Free Talk, or usual care (UC). The authors examined client acceptance, and intervention feasibility and conducted a preliminary outcome evaluation. Free Talk teens reported higher quality and satisfaction ratings, and MI integrity scores were higher for Free Talk groups. AOD use and delinquency decreased for both groups at 3 months, and 12-month recidivism rates were lower but not significantly different for the Free Talk group compared to UC. Results contribute to emerging literature on MI in a group setting. A longer term follow-up is warranted.

**Substance-Use Disorders and Poverty As Prospective Predictors Of First-Time Homelessness In the United States** Thompson Jr, RG, Wall MM, Greenstein E, Grant BF, Hasin DS. Am J Public Health. 2013; 103 Suppl 2: S282-288.

The authors examined whether substance-use disorders and poverty predicted first-time homelessness over 3 years. They analyzed longitudinal data from waves 1 (2001-2002) and 2 (2004-2005) of the National Epidemiologic Survey on Alcohol and Related Conditions to determine the main and interactive effects of wave 1 substance use disorders and poverty on first-time homelessness by wave 2, among those who were never homeless at wave 1 ( $n = 30,558$ ). First-time homelessness was defined as having no regular place to live or having to live with others for 1 month or more as a result of having no place of one's own since wave 1. Alcohol-use disorders (adjusted odds ratio [AOR] = 1.34), drug-use disorders (AOR = 2.51), and poverty (AOR = 1.34) independently increased prospective risk for first-time homelessness, after adjustment for ecological variables. Substance-use disorders and poverty interacted to differentially influence risk for first-time homelessness ( $P < .05$ ), before, but not after, adjustment for controls. This study reinforces the importance of both substance-use disorders and poverty in the risk for first-time homelessness, and can serve as a benchmark for future studies. Substance abuse treatment should address financial status and risk of future homelessness.

**Cortisol At the Emergency Room Rape Visit As A Predictor Of PTSD and Depression Symptoms Over Time** Walsh K, Nugent NR, Kotte A, Amstadter AB, Wang S, Guill C, Acierno R, Kilpatrick DG, Resnick HS. Psychoneuroendocrinology. 2013; 38(11): 2520-2528.

Dysregulation of the hypothalamic-pituitary-adrenal axis, typically reflected by alterations in cortisol responsively, has been associated with exposure to traumatic events and the development of stress-related disorders such as posttraumatic stress disorder (PTSD) and depression. Serum cortisol was measured at the time of a post sexual assault medical exam among a sample of 323 female victims of recent sexual assault. Analyses were conducted among 235 participants who provided data regarding history of previous assault as well as PTSD and depression symptoms during at least one of the three follow-ups. Growth curve models suggested that prior history of assault and serum cortisol were positively associated with the intercept and negatively associated with the slope of PTSD and depression symptoms after controlling for covariates. Prior history of assault and serum cortisol also interacted to predict the intercept and slope of PTSD and depression symptoms such that women with a prior history of assault and lower ER cortisol had higher initial symptoms that decreased at a slower rate relative to women without a prior history and those with higher ER cortisol. Prior history of assault was associated with diminished acute cortisol responsively at the emergency room visit. Prior assault history and cortisol both independently and interactively predicted PTSD and depression symptoms at first follow-up and over the course a 6-month follow-up.

**Interactive Effects Of Drinking History and Impulsivity On College Drinking** Adams ZW, Milich R, Lynam DR, Charnigo RJ. Addict Behav. 2013; 38(12): 2860-2867.

The transition from adolescence into emerging adulthood is a critical developmental period for changes in alcohol use and drinking related problems. Prior research has identified a number of distinct developmental alcohol use trajectories, which appear to be differentially related to young adult drinking outcomes. Another correlate of alcohol use in early adulthood is impulsivity. The primary aim of this study was to examine the moderating role of impulsivity in the relation between patterns of past alcohol use and hazardous drinking during the first year of college. Participants ( $N=452$ ; 49% male; mean age 18.5 years; 82% Caucasian) completed self-report measures during the first year of college, including retrospective alcohol use calendars, current alcohol use and drinking problems, and personality. Group-based trajectory modeling was used to identify groups with similar adolescent drinking history from retrospective, self-report. Four groups were identified: abstainers/very light

users, late/moderate users, early/moderate users, and steep increase/heavy users. The abstainer/very light user group reported the lowest levels of alcohol use and problematic drinking in college; the steep increase/heavy use group reported the highest levels of alcohol use and problematic drinking. As predicted, the role of personality-specific urgency, or emotion-based rash action-was strongest among moderate use groups. These findings may be helpful in guiding targeted prevention and intervention programs for alcohol use and abuse.

**Understanding the Link Between Early Sexual Initiation and Later Sexually Transmitted Infection: Test and Replication in Two Longitudinal Studies**

Epstein M, Bailey JA, Manhart LE, Hill KG, Hawkins JD, Haggerty KP, Catalano RF. *J Adolesc Health*. 2014 April; 54(4): 435-446. Age at sexual initiation is strongly associated with sexually transmitted infections (STI); yet, prevention programs aiming to delay sexual initiation have shown mixed results in reducing STI. This study tested three explanatory mechanisms for the relationship between early sexual debut and STI: number of sexual partners, individual characteristics, and environmental antecedents. A test-and-replicate strategy was employed using two longitudinal studies: the Seattle Social Development Project (SSDP) and Raising Healthy Children (RHC). Childhood measures included pubertal age, behavioral disinhibition, and family, school, and peer influences. Alcohol use and age of sexual debut were measured during adolescence. Lifetime number of sexual partners and having sex under the influence were measured during young adulthood. Sexually transmitted infection diagnosis was self-reported at age 24. Early sex was defined as debut at <15 years. Path models were developed in SSDP evaluating relationships between measures, and were then tested in RHC. The relationship between early sex and STI was fully mediated by lifetime sex partners in SSDP, but only partially in RHC, after accounting for co-occurring factors. Behavioral disinhibition predicted early sex, early alcohol use, number of sexual partners, and sex under the influence, but had no direct effect on STI. Family management protected against early sex and early alcohol use, whereas antisocial peers exacerbated the risk. Early sexual initiation, a key mediator of STI, is driven by antecedents that influence multiple risk behaviors. Targeting co-occurring individual and environmental factors may be more effective than discouraging early sexual debut and may concomitantly improve other risk behaviors.

**Current Cigarette Smoking Among HIV-Positive Current and Former Drug Users: Associations With Individual and Social Characteristics**

Pacek LR, Latkin C, Crum RM, Stuart EA, Knowlton AR. *AIDS Behav*. 2013 Nov 28 [e-pub ahead of print]. Cigarette smoking is endemic among HIV-positive populations and is related to substantial morbidity and mortality. Research has largely focused on individual-level characteristics associated with smoking, with less attention to social factors. The authors aimed to explore individual- and social-level characteristics associated with current cigarette smoking among people living with HIV. Data came from 358 individuals on antiretroviral therapy interviewed in a study on informal HIV caregiving, conducted in Baltimore, MD, USA. Most participants (75%) were current smokers and 45% reported current illegal drug use. In adjusted logistic regression analyses, current drug use (aOR 2.90, 95% CI 1.58-5.30), 12-step program participation (aOR 1.74, 95% CI 1.02-2.97), and having a main Supporter who is a current smoker (aOR 1.93, 95% CI 1.12-3.33) were associated with current smoking. Findings suggest the importance of social-level factors in cigarette smoking among HIV seropositive drug users and have implications for developing targeted smoking cessation interventions for smokers living with HIV.

### **Objective and Perceived Neighborhood Characteristics and Tobacco Use Among Young Adults**

Brown QL, Milam AJ, Smart MJ, Johnson RM, Linton SL, Furr-Holden CDM, Ialongo NS. *Drug Alcohol Depend.* 2014; 134: 370-375.

In the US, past month tobacco use is higher among young adults aged 18-25 years than among any other age group. Neighborhood disorder may be a malleable environmental determinant of tobacco use among young adults; its correlation with tobacco use is understudied. The purpose of this study was to examine whether perceived and objectively measured neighborhood factors are associated with tobacco use among young adults in Baltimore City. This cross-sectional study of predominately African American young adults (n=359) used logistic regression models via generalized estimating equations (GEE) to estimate the association of perceived and objective neighborhood disorder with past month tobacco use, adjusting for race, age, sex, income, and other substance use. Two measures of perceived neighborhood environment - neighborhood drug involvement, and neighborhood social cohesion - were derived from the Neighborhood Environment Scale (NES). Objective neighborhood disorder was measured via trained field raters using the Neighborhood Inventory for Environmental Typology (NifETy) instrument. Sex modified the relationship between perceived neighborhood drug involvement and past month tobacco use, and the association was significant among women only (aOR=1.49; 95% CI=1.19-1.88). Perceptions of neighborhood social cohesion (aOR=0.97; 95% CI=0.83-1.13), and objective neighborhood disorder (aOR=1.17; 95% CI=0.98-1.38) were not significantly associated with past month tobacco use. Understanding the correlation between perceived and objective neighborhood disorder, and their independent association with tobacco use can potentially lead to environmentally based interventions aimed at reducing tobacco use among young adults who live in urban environments.

**Friendship Group Position and Substance Use** Osgood DW, Feinberg ME, Wallace LN, Moody J. *Addict Behav.* 2014 May; 39(5): 922-933.

This paper examines how an adolescent's position relative to cohesive friendship groups in the school-wide social network is associated with alcohol, tobacco, and marijuana use. The authors extend prior research in this area by refining the categories of group positions, using more extensive friendship information, applying newer analytic methods to identify friendship groups, and making strategic use of control variables to clarify the meaning of differences among group positions. They report secondary analyses of 6th through 9th grade data from the PROSPER study, which include approximately 9500 adolescents each year from 27 school districts and 368 school grade cohort friendship networks. They find that core members of friendship groups were more likely to drink than isolates and liaisons, especially in light of their positive social integration in school, family, and religious contexts. Isolates were more likely to use cigarettes than core members, even controlling for all other factors. Finally, liaisons were more likely to use marijuana than core members.

### **Assessment Of Club Patrons' Alcohol and Drug Use: The Use Of Biological Markers**

Miller BA, Byrnes HF, Branner AC, Voas R, Johnson MB. *Am J Prev Med.* 2013; 45(5): 637-643.

Young adulthood (ages 18-25 years) represents a time when high-risk behaviors, including alcohol and drug use, peak. Electronic music dance events (EMDEs) featured at clubs provide an ecologic niche for these high-risk behaviors. This paper examines the prevalence of alcohol and drug use among EMDE patrons. Examination of personal characteristics associated with exit levels of alcohol and drug use identifies important indicators of risk taking for prevention strategies. Data were collected anonymously during 2010-2012 from 2028 patrons as they entered and exited clubs in the San Francisco Bay area featuring EMDEs. Nearly half were aged 25 years. Biological measures of drug and alcohol and self-reported personal characteristics were attained. Analyses were completed in 2012. At entrance, more than one fifth of patrons were positive for drug use and one fourth arrived

either impaired (blood alcohol concentration [BAC]: 0.05%-0.079%) or intoxicated (BAC: >0.08%) by alcohol. At exit, one fourth tested positive for drugs, and nearly half were impaired or intoxicated by alcohol. Individual characteristics that were important for levels of risk included prior alcohol use behaviors, sexual identity, ethnic/racial identity, and transportation to the event. Gender did not differentiate for alcohol use but fewer women used drugs. Findings confirm the importance of targeting EMDEs for prevention efforts. EMDEs attract young working adults who are engaged in heavy alcohol and/or drug use. Targeting these social settings for delivering public health prevention strategies regarding alcohol and drug use and related harm is indicated by the findings.

### **Sexual Risk Behavior and STI Health Literacy Among Ethnic Minority Adolescent Women**

Dimmitt Champion J, Harlin B, Collins JL. Appl Nurs Res. 2013; 2 (4): 204-209.

Although information is available for prevention of sexually transmitted infection (STI/HIV), adolescents continue to engage in high risk sexual behavior particularly ethnic minority adolescent women with histories of STI or abuse. A description therefore of STI/HIV knowledge and sexual risk behavior among these women is indicated for modification of prevention efforts for sexual health promotion. African-American (n=94) and Mexican-American (n=465) adolescent women 14-18 years of age were included in the study. Assessments of sexual risk behavior and STI/HIV knowledge among these adolescent women described Mexican-American women as at higher risk of STI, pregnancy, substance use and abuse with lower levels of STI/HIV knowledge, previous HIV testing and perceptions of risk than African-American women. A focus on Mexican-American adolescent women with histories of STI and abuse is indicated for translation of community-based health promotion interventions for amelioration of potential adverse sexual health outcomes among ethnic minority adolescent women.

### **Parental Monitoring Trajectories and Gambling Among A Longitudinal Cohort Of Urban Youth**

Lee GP, Stuart EA, Ialong NS, Martins SS. Addiction. 2013 Nov 6 [e-pub ahead of print].

The aim of this study was to test the strength of the association between parental monitoring trajectories throughout early adolescence (ages 11-14) and gambling behaviors by young adulthood (age 22). Longitudinal cohort design. Baltimore, Maryland. The sample of 514 participants with gambling data between ages 16-22 and parental monitoring data between ages 11-14 were predominantly African American and received subsidized lunches at age 6. The South Oaks Gambling Screen and South Oaks Gambling Screen-Revised for Adolescents collected self-reports on annual gambling and gambling problems between ages 16-22. The Parental Monitoring Subscale of the Structured Interview of Parent Management Skills and Practices-Youth Version collected self-reports on annual parental monitoring between ages 11-14. General growth mixture modelling identified two parental monitoring trajectories: (i) "stable" class (84.9%) began with a high level of parental monitoring at age 11 that remained steady to age 14; (ii) "declining" class (15.1%) began with a significantly lower level of parental monitoring at age 11 and experienced a significant to through age 14. The declining class had increased significantly unadjusted (OR=1.91; 95% CI=1.59, 2.23; P=0.001) and adjusted (aOR=1.57; 95% CI=1.24, 1.99; P=0.01) odds of problem gambling compared with non-gambling. Low and/or declining parental monitoring of children between the ages of 11 and 14 is associated significantly with problem gambling when those children reach young adulthood.

### **Intergenerational Sex As A Risk Factor For HIV Among Young Men Who Have Sex With Men: A Scoping Review**

Anema A, Marshall BDL, Stevenson B, Gurm J, Montaner G, Small W, Roth EA, Lima VD, Montaner JSG, Moore D, Hogg RS. Curr HIV/AIDS Rep. 2013; 10(4): 398-407.

An emerging body of evidence suggests that intergenerational sexual partnerships may increase risk of HIV acquisition among young men who have sex with men (YMSM). However, no studies have

comprehensively evaluated literature in this area. The authors applied a scoping review methodology to explore the relationships between age mixing, HIV risk behavior, and HIV seroconversion among YMSM. This study identified several individual, micro-, and meso-system factors influencing HIV risk among YMSM in the context of intergenerational relationships: childhood maltreatment, coming of age and sexual identity, and substance use (individual-level factors); family and social support, partner characteristics, intimate partner violence, connectedness to gay community (micro-system factors); and race/ethnicity, economic disparity, and use of the Internet (meso-system factors). These thematic groups can be used to frame future research on the role of age-discrepant relationships on HIV risk among YMSM, and to enhance public health HIV education and prevention strategies targeting this vulnerable population.

**Investigating the Potential Causal Relationship Between Parental Knowledge and Youth Risky Behavior: A Propensity Score Analysis** Lippold MA, Coffman DL, Greenberg MT. *Prev Sci.* 2013 Nov 30 [e-pub ahead of print].

This longitudinal study aims to explore the potential causal relationship between parental knowledge and youth risky behavior among a sample of rural, early adolescents (84% White, 47% male). Using inverse propensity weighting, the sample was adjusted by controlling for 33 potential confounding variables. Confounding variables include other aspects of the parent-child relationship, parental monitoring, demographic variables, and earlier levels of problem behavior. The effect of parental knowledge was significant for youth substance and poly substance use initiation, alcohol and cigarette use, attitudes towards substance use, and delinquency. These results suggest that parental knowledge may be causally related to substance use during middle school, as the relationship between knowledge and youth outcomes remained after controlling for 33 different confounding variables. The discussion focuses on understanding issues of causality in parenting and intervention implications.

**Neural Basis Of Emotional Decision Making In Trait Anxiety** Xu P, Gu R, Broster LS, Wu R, Van Dam NT, Jiang Y, Fan J, Luo Y-J. *J Neurosci.* 2013; 33(47): 18641-18653.

Although trait anxiety has been associated with risk decision making, whether it is related to risk per se or to the feeling of the risk, as well as the underlying neurocognitive mechanisms, remains unclear. Using a decision-making task with a manipulation of frame (i.e., written description of options as a potential gain or loss) and functional magnetic resonance imaging, the authors investigated the neurocognitive relationship between trait anxiety and decision making. The classic framing effect was observed: participants chose the safe option when it was described as a potential gain, but they avoided the same option when it was described as a potential loss. Most importantly, trait anxiety was positively correlated with this behavioral bias. Trait anxiety was also positively correlated with amygdala-based "emotional" system activation and its coupling with the ventromedial prefrontal cortex (vmPFC) when decisions were consistent with the framing effect, but negatively correlated with the dorsal anterior cingulate cortex (dACC)-based "analytic" system activation and its connectivity to the vmPFC when decisions ran counter to the framing effect. These findings suggest that trait anxiety is not associated with subjective risk preference but an evaluative bias of emotional information in decision making, underpinned by a hyperactive emotional system and a hypoactive analytic system in the brain.

**Association Between Work-Family Conflict and Smoking Quantity Among Daily Smokers** Macy JT, Chassin L, Presson CC. *Nicotine Tob Res.* 2013; 15(11): 1867-1872.

Recent work demonstrated a direct relation between work-family conflict and likelihood of smoking. This study furthered this area of research by (a) testing the association between work-family conflicts and smoking quantity and (b) testing demographic, workplace, and home factors as moderators of this

relation. Participants (N = 423) were daily smokers from a Midwestern community-based sample. Ordinal regression analysis tested work-to-home and home-to-work conflict as predictors (after controlling for demographic characteristics, home factors, and workplace factors) of smoking quantity. Additionally, the authors tested whether the demographic, home, and workplace factors moderated the effects of work-to-home conflict and home-to-work conflict on smoking quantity. Males (OR = 8.81,  $p = .005$ ), older participants (OR = 1.09,  $p = .012$ ), those with less educational attainment (OR = 1.87,  $p = .001$ ), those who reported lower levels of workplace smoking restrictions (OR = 0.87,  $p = .019$ ), and those who reported higher levels of work-to-home conflict (OR = 1.39,  $p = .026$ ) smoked more cigarettes per day. There was no significant main effect of home-to-work conflict on smoking quantity (OR = 1.46,  $p = .099$ ). A significant interaction (OR = 0.55,  $p = .043$ ) revealed that home-to-work conflict was associated with smoking quantity for females but not for males. After controlling for demographic characteristics and potential confounders, work-to-home conflict had a negative impact on smoking quantity for all participants, and home-to-work conflict was associated with smoking quantity for women. Workplace wellness programs to reduce smoking among employees should take into account the direction of conflict and how the effect of the conflict on smoking behavior may vary based on other factors.

**High Frequency Of False-Positive Hepatitis C Virus Enzyme-Linked Immunosorbent Assay In Rakai, Uganda** Mullis CE, Laeyendecker O, Reynolds SJ, Ocama P, Quinn J, Boaz I, Gray RH, Kirk GD, Thomas DL, Quinn TC, Stabinski L. Clin Infect Dis. 2013; 57(12): 1747-1750.

The prevalence of hepatitis C virus (HCV) infection in sub-Saharan Africa remains unclear. The authors tested 1000 individuals from Rakai, Uganda, with the Ortho version 3.0 HCV enzyme-linked immunosorbent assay. All serologically positive samples were tested for HCV RNA. Seventy-six of the 1000 (7.6%) participants were HCV antibody positive; none were confirmed by detection of HCV RNA.

**Typology Of Alcohol Users Based On Longitudinal Patterns Of Drinking** Harrington M, Velicer WF, Ramsey S. Addict Behav. 2014; 39(3): 607-621.

Worldwide, alcohol is the most commonly used psychoactive substance. However, heterogeneity among alcohol users has been widely recognized. This paper presents a typology of alcohol users based on an implementation of idiographic methodology to examine longitudinal daily and cyclic (weekly) patterns of alcohol use at the individual level. A secondary data analysis was performed on the pre-intervention data from a large randomized control trial. A time series analysis was performed at the individual level, and a dynamic cluster analysis was employed to identify homogenous longitudinal patterns of drinking behavior at the group level. The analysis employed 180 daily observations of alcohol use in a sample of 177 alcohol users. The first order autocorrelations ranged from  $-.76$  to  $.72$ , and seventh order autocorrelations ranged from  $-.27$  to  $.79$ . Eight distinct profiles of alcohol users were identified, each characterized by a unique configuration of first and seventh autoregressive terms and longitudinal trajectories of alcohol use. External validity of the profiles confirmed the theoretical relevance of different patterns of alcohol use. Significant differences among the eight subtypes were found on gender, marital status, frequency of drug use, lifetime alcohol dependence, family history of alcohol use and the Short Index of Problems. Our findings demonstrate that individuals can have very different temporal patterns of drinking behavior. The daily and cyclic patterns of alcohol use may be important for designing tailored interventions for problem drinkers.



**Retrospective Chart Review For Obesity and Associated Interventions Among Rural Mexican-American Adolescents Accessing Healthcare Services** Champion JD, Collins JL. J Am Assoc Nurse Pract. 2013; 25(11): 604-610.

The aim of this paper was to report a retrospective analysis of data routinely collected in the course of healthcare services at a rural health clinic and to assess obesity incidence and associated interventions among rural Mexican-American adolescents. Two hundred and twelve charts reviewed; 98 (46.2%) males and 114 (53.8%) females. Data extracted included Medicaid exams conducted at the clinic within 5 years. Equal overweight or obese (n = 105, 49.5%), versus normal BMI categorizations (n = 107, 50.5%) documented overall and by gender. Female obesity higher (25.4%) than national norms (17.4%); male rates (25.5%) were within national norm. Interventions provided by nurse practitioners (94%) for 34.8%-80% of overweight/obese had limited follow-up (4%). Obesity incidence markedly increased between 13 and 18 years of age without associated interventions; 51.4%-75.6% without interventions. Obesity is a healthcare problem among rural Mexican-American adolescents accessing care at the rural health clinic. Obesity intervention and follow-up was suboptimal within this setting. Rural and ethnic minority adolescents experience health disparities concerning obesity prevalence and remote healthcare access. Obesity prevention and treatment during adolescence is a national health priority given physiologic and psychological tolls on health and potential for obesity into adulthood. Obesity assessment and translation of evidence-based interventions for rural Mexican-American adolescents at rural health clinics is implicated.

**A Continuum Of Approaches Toward Developing Culturally Focused Prevention Interventions: From Adaptation To Grounding** Okamoto SK, Kulis S, Marsiglia FF, Holleran Steiker LK, Dustman P. J Prim Prev. 2014 April; 35(2): 103-112.

The purpose of this article is to describe a conceptual model of methods used to develop culturally focused interventions. The authors describe a continuum of approaches ranging from non-adapted/surface-structure adapted programs to culturally grounded programs, and present recent examples of interventions resulting from the application of each of these approaches. The model has implications for categorizing culturally focused prevention efforts more accurately, and for gauging the time, resources, and level of community engagement necessary to develop programs using each of the different methods. The model also has implications for funding decisions related to the development and evaluation of programs, and for planning of participatory research approaches with community members.

**Young Adult Follow-Up Of Adolescent Girls In Juvenile Justice Using The Columbia Suicide Severity Rating Scale** Kerr DC, Gibson B, Leve LD, Degarmo DS. Suicide Life Threat Behav. 2014 April; 44(2): 113-129.

This study focused on the reliability and validity of the Columbia Suicide Severity Scale (C-SSRS). Severely delinquent adolescent girls (n=166) participated in a treatment trial and repeated assessments over time. Lifetime suicide attempt history was measured using the C-SSRS in early adulthood (n=144; 7-12 years post baseline). Nonclinical raters showed strong interrater reliability using the C-SSRS. Self-reports, caseworker reports, and caregiver reports of girls' suicide attempt histories collected at baseline correlated with adult participants' recollections of their baseline attempt histories. Suicidal ideation measured prospectively across a 7- to -12-year period was associated with retrospectively reported suicide attempt across the same period.

**Drawing Causal Inferences Using Propensity Scores: A Practical Guide For Community Psychologists**

Lanza ST, Moore JE, Butera NM. Am J Community Psychol. 2013; 52(3-4): 380-392. Confounding present in observational data impede community psychologists' ability to draw causal inferences. This paper describes propensity score methods as a conceptually straightforward approach to drawing causal inferences from observational data. A step-by-step demonstration of three propensity score methods-weighting, matching, and sub classification-is presented in the context of an empirical examination of the causal effect of preschool experiences (Head Start vs. parental care) on reading development in kindergarten. Although the unadjusted population estimate indicated that children with parental care had substantially higher reading scores than children who attended Head Start, all propensity score adjustments reduce the size of this overall causal effect by more than half. The causal effect was also defined and estimated among children who attended Head Start. Results provide no evidence for improved reading if those children had instead received parental care. The authors carefully define different causal effects and discuss their respective policy implications, summarize advantages and limitations of each propensity score method, and provide SAS and R syntax so that community psychologists may conduct causal inference in their own research.

## **BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH**

### **Exploring the Feasibility of Text Messaging to Support Substance Abuse Recovery among Youth in Treatment**

Gonzales R1, Douglas Anglin M, Glik DC. Health Educ Res. 2014 Feb; 29(1): 13-22. This exploratory study examined treatment involved youth opinions about (i) the utility of using text messaging to support recovery behaviors after treatment; (ii) important types of text messages that could help youth self-manage their substance use behaviors after treatment; and (iii) programmatic or logistical areas associated with text messaging programs. Eight focus groups were conducted with 67 youth (aged 12-24) enrolled in outpatient and residential publicly funded substance abuse treatment programs around Los Angeles County, California. Results highlight that 70% of youth positively endorsed text messaging as a viable method of intervention during aftercare, 20% expressed ambivalent feelings, and 10% conveyed dislike. Thematic data exploration revealed seven themes related to the types of text messages youth recommend for helping youth avoid relapse after treatment, including positive appraisal (90%), lifestyle change tips (85%), motivational reinforcing (80%), coping advice (75%), confidence boosters (65%), inspiration encouragement (55%), and informational resources (50%). Youth opinions about key logistical features of text messaging programs, including frequency, timing, sender, and length are also examined. Findings offer insight for the development and enhancement of recovery support interventions with substance abusing youth. Results imply text messaging may serve as a promising opportunity for recovery support for young people with substance abuse problems.

### **A Double Blind, within Subject Comparison of Spontaneous Opioid Withdrawal from Buprenorphine Versus Morphine**

Tompkins DA, Smith MT, Mintzer MZ, Campbell CM, Strain EC. J Pharmacol Exp Ther. 2014 Feb; 348(2): 217-226.

Preliminary evidence suggests that there is minimal withdrawal after the cessation of chronically administered buprenorphine and that opioid withdrawal symptoms are delayed compared with those of other opioids. The present study compared the time course and magnitude of buprenorphine withdrawal with a prototypical  $\mu$ -opioid agonist, morphine. Healthy, out-of-treatment opioid-dependent residential volunteers (N = 7) were stabilized on either buprenorphine (32 mg/day i.m.) or morphine (120 mg/day i.m.) administered in four divided doses for 9 days. They then underwent an 18-day period of spontaneous withdrawal, during which four double-blind i.m. placebo injections were administered daily. Stabilization and spontaneous withdrawal were assessed for the second opioid using the same time course. Opioid withdrawal measures were collected eight times daily. Morphine withdrawal symptoms were significantly ( $P < 0.05$ ) greater than those of buprenorphine withdrawal as measured by mean peak ratings of Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), all subscales of the Profile of Mood States (POMS), sick and pain (0-100) Visual Analog Scales, systolic and diastolic blood pressure, heart rate, respiratory rate, and pupil dilation. Peak ratings on COWS and SOWS occurred on day 2 of morphine withdrawal and were significantly greater than on day 2 of buprenorphine withdrawal. Subjective reports of morphine withdrawal resolved on average by day 7. There was minimal evidence of buprenorphine withdrawal on any measure. In conclusion, spontaneous withdrawal from high-dose buprenorphine appears subjectively and objectively milder compared with that of morphine for at least 18 days after drug cessation.

**The Effect of Repeated Intramuscular Alfentanil Injections on Experimental Pain and Abuse Liability Indices in Healthy Males**

Tompkins DA, Smith MT, Bigelow GE, Moaddel R, Venkata SL, Strain EC. Clin J Pain. 2014 Jan; 30(1): 36-45.

Opioid-induced hyperalgesia (OIH), increased sensitivity to noxious stimuli after repeated opioid exposures, has been demonstrated in preclinical studies. However, there is no accepted, prospective model of OIH after repeated opioid exposures currently available in humans. This study assessed a potential prospective OIH model. Double-blind intramuscular injections of a short-acting opioid (alfentanil 15 mcg/kg; N=8) were compared to active placebo (diphenhydramine 25 mg; N=3) on cold and pressure pain testing and standard abuse liability measures in eight 10-hour sessions (1 injection/session) over 4 to 5 weeks in healthy, pain-free males. Decreases from session baseline pain threshold (PThr) and tolerance (PTol) were calculated to represent hyperalgesia, and were assessed both within and across sessions. Mean decreases in cold PTol were seen in the alfentanil group at 180 minutes (-3.8 s,  $\pm 26.5$ ) and 480 minutes (-1.63 s,  $\pm 31.5$ ) after drug administration. There was a trend for differences between conditions on cold PThr hyperalgesia but not for pressure PThr. Alfentanil participants had greater mean ratings on Liking and High visual analog scales at peak effects (30 min), but these scores did not change across sessions. Repeated alfentanil exposures over 4 to 5 weeks resulted in within session decreases in cold pain tolerance from baseline but these differences were not substantially different from diphenhydramine controls. The results did not support the phenomenon of OIH in this model, although definitive conclusions regarding the existence of OIH in humans likely requires a larger sample size or an alternative model.

**Cannabis Use Behaviors and Social Anxiety: The Roles of Perceived Descriptive and Injunctive Social Norms**

Ecker AH, Buckner JD. J Stud Alcohol Drugs. 2014 Jan; 75(1): 74-82.

Individuals with greater social anxiety are particularly vulnerable to cannabis-related impairment. Descriptive norms (beliefs about others' use) and injunctive norms (beliefs regarding others' approval of risky use) may be particularly relevant to cannabis-related behaviors among socially anxious persons if they use cannabis for fear of evaluation for deviating from what they believe to be normative behaviors. Yet, little research has examined the impact of these social norms on the relationships between social anxiety and cannabis use behaviors. The current study investigated whether the relationships of social anxiety to cannabis use and use-related problems varied as a function of social norms. The sample comprised 230 (63.0% female) current cannabis-using undergraduates. Injunctive norms (regarding parents, not friends) moderated the relationship between social anxiety and cannabis-related problem severity. Post hoc probing indicated that among participants with higher (but not lower) social anxiety, those with greater norm endorsement reported the most severe impairment. Injunctive norms (parents) also moderated the relationship between social anxiety and cannabis use frequency such that those with higher social anxiety and lower norm endorsement used cannabis less frequently. Descriptive norms did not moderate the relationship between social anxiety and cannabis use frequency. Socially anxious cannabis users appear to be especially influenced by beliefs regarding parents' approval of risky cannabis use. Results underscore the importance of considering reference groups and the specific types of norms in understanding factors related to cannabis use behaviors among this vulnerable population.

**Homelessness, Cigarette Smoking and Desire to Quit: Results from a US National Study**

Baggett TP1, Lebrun-Harris LA, Rigotti NA. Addiction. 2013 Nov; 108(11): 2009-2018.

The authors determined whether or not homelessness is associated with cigarette smoking independent of other socio-economic measures and behavioral health factors, and whether homeless smokers differ from non-homeless smokers in their desire to quit. They analyzed data from 2678 adult respondents to the 2009 Health Center Patient Survey, a nationally representative cross-sectional survey of homeless

and non-homeless individuals using US federally funded community health centers. They used multivariable logistic regression to examine the association between homelessness and (i) current cigarette smoking among all adults, and (ii) past-year desire to quit among current smokers, adjusting for demographic, socio-economic and behavioral health characteristics. Adults with any history of homelessness were more likely than never homeless respondents to be current smokers (57 versus 27%,  $P < 0.001$ ). In multivariable models, a history of homelessness was associated independently with current smoking [adjusted odds ratio (AOR) 2.09; 95% confidence interval (CI) = 1.49-2.93], even after adjusting for age, sex, race, veteran status, insurance, education, employment, income, mental illness and alcohol and drug abuse. Housing status was not associated significantly with past-year desire to stop smoking in unadjusted ( $P = 0.26$ ) or adjusted ( $P = 0.60$ ) analyses; 84% of currently homeless, 89% of formerly homeless and 82% of never homeless smokers reported wanting to quit. Among patients of US health centers, a history of homelessness doubles the odds of being a current smoker independent of other socio-economic factors and behavioral health conditions. However, homeless smokers do not differ from non-homeless smokers in their desire to quit and should be offered effective interventions.

**Young Adults Who Smoke Cigarettes and Marijuana: Analysis of Thoughts and Behaviors** Ramo DE, Delucchi KL, Liu H, Hall SM, Prochaska JJ. *Addict Behav.* 2014 Jan; 39(1): 77-84.

Smoking both cigarettes and marijuana is increasingly common among young adults, yet little is known about use patterns, motivations, or thoughts about abstinence. In a U.S. sample, this study explored young adults' severity of cigarette and marijuana co-use, quit attempts, and thoughts about use. Young adults age 18-to-25 who had smoked at least one cigarette in the past 30 days completed an anonymous online survey. Of 1987 completed surveys, 972 participants reported both past-month cigarette and marijuana use (68% male, 71% Caucasian, mean age 20.4 years [SD=2.0]). Frequency of use, temptations to use, measures of dependence, decisional balance, and past-year quit attempts were associated across the two substances (all  $p < .05$ ), but not motivation to quit. Relative to marijuana, participants reported greater desire and a later stage of change for quitting cigarettes and were more likely to endorse a cigarette abstinence goal, yet they had lower expectancy of success with quitting cigarettes and with staying quit (all  $p < .001$ ). Cigarette and marijuana use, temptations to use, and pros/cons of using were related in this young adult sample. Differences in motivation and thoughts about abstinence, however, suggest that young adults may be more receptive to interventions for tobacco than marijuana use. Use patterns and cognitions for both substances should be considered in prevention and intervention efforts.

**Cost-effectiveness of Extended Cessation Treatment for Older Smokers** Barnett PG1, Wong W, Jeffers A, Munoz R, Humfleet G, Hall S. *Addiction.* 2014 Feb; 109(2): 314-322.

The authors examined the cost-effectiveness of extended smoking cessation treatment in older smokers. Participants who completed a 12-week smoking cessation program were factorial randomized to extended cognitive behavioral treatment and extended nicotine replacement therapy. The study setting was a free-standing smoking cessation clinic. Participants comprised a total of 402 smokers aged 50 years and older who were recruited from the community. The trial measured biochemically verified abstinence from cigarettes after 2 years and the quantity of smoking cessation services utilized. Trial findings were combined with literature on changes in smoking status and the age- and gender-adjusted effect of smoking on health-care cost, mortality and quality of life over the long term in a Markov model of cost-effectiveness over a lifetime horizon. The addition of extended cognitive behavioral therapy added \$83 in smoking cessation services cost [ $P = 0.012$ , confidence interval (CI) = \$22-212]. At the end of follow-up, cigarette abstinence rates were 50.0% with extended

cognitive behavioral therapy and 37.2% without this therapy ( $P < 0.05$ , odds ratio 1.69, CI 1.18-2.54). The model-based incremental cost-effectiveness ratio was \$6324 per quality-adjusted life year (QALY). Probabilistic sensitivity analysis found that the additional \$947 in lifetime cost of the intervention had a 95% confidence interval of -\$331 to 2081; the 0.15 additional QALYs had a confidence interval of 0.035-0.280, and that the intervention was cost-effective against a \$50 000/QALY acceptance criterion in 99.6% of the replicates. Extended nicotine replacement therapy was not cost-effective. The authors conclude that adding extended cognitive behavior therapy to standard cessation treatment was cost-effective. Further intensification of treatment may be warranted.

**Computer-Assisted Delivery of Cognitive-Behavioral Therapy: Efficacy and Durability of CBT4CBT Among Cocaine-Dependent Individuals Maintained on Methadone** Carroll KM, Kiluk BD, Nich C, Gordon MA, Portnoy GA, Marino DR, Ball SA. Am J Psychiatry. 2014 Feb 28. doi: 10.1176/appi.ajp.2013.13070987. [Epub ahead of print].

A previous pilot trial evaluating computer-based training for cognitive-behavioral therapy (CBT4CBT) in 77 heterogeneous substance users (alcohol, marijuana, cocaine, and opioids) demonstrated preliminary support for its efficacy in the context of a community-based outpatient clinic. The authors conducted a more definitive trial in a larger, more homogeneous sample. In this randomized clinical trial, 101 cocaine-dependent individuals maintained on methadone were randomly assigned to standard methadone maintenance or methadone maintenance with weekly access to CBT4CBT, with seven modules delivered within an 8-week trial. Treatment retention and data availability were high and comparable across the treatment conditions. Participants assigned to the CBT4CBT condition were significantly more likely to attain 3 or more consecutive weeks of abstinence from cocaine (36% compared with 17%;  $p < 0.05$ , odds ratio=0.36). The group assigned to CBT4CBT also had better outcomes on most dimensions, including urine specimens negative for all drugs, but these reached statistical significance only for individuals completing the 8-week trial ( $N=69$ ). Follow-up data collected 6 months after treatment termination were available for 93% of the randomized sample; these data indicate continued improvement for those assigned to the CBT4CBT group, replicating previous findings regarding its durability. This trial replicates earlier findings indicating that CBT4CBT is an effective adjunct to addiction treatment with durable effects. CBT4CBT is an easily disseminable strategy for broadening the availability of CBT, even in challenging populations such as cocaine-dependent individuals enrolled in methadone maintenance programs.

**Mobile Contingency Management as an Adjunctive Smoking Cessation Treatment for Smokers with Posttraumatic Stress Disorder** Hertzberg JS1, Carpenter VL, Kirby AC, Calhoun PS, Moore SD, Dennis MF, Dennis PA, Dedert EA, Beckham JC. Nicotine Tob Res. 2013 Nov; 15(11): 1934-1938.

Smokers with posttraumatic stress disorder (PTSD) smoke at higher prevalence rates and are more likely to relapse early in a quit attempt. Innovative methods are needed to enhance quit rates, particularly in the early quit period. Web-based contingency-management (CM) approaches have been found helpful in reducing smoking among other difficult-to-treat smoker populations but are limited by the need for computers. This pilot study builds on the web-based CM approach by evaluating a smartphone-based application for CM named mobile CM (mCM). Following a 2-week training period, 22 smokers with PTSD were randomized to a 4-week mCM condition or a yoked (i.e., noncontingent 4-week mCM condition). All smokers received 2 smoking cessation counseling sessions, nicotine replacement, and bupropion. Participants could earn up to \$690 (\$530 for mCM, \$25.00 for assessments and office visits [up to 5], and \$35.00 for equipment return). The average earned was \$314.00. Compliance was high during the 2-week training period (i.e., transmission of videos) (93%) and the 4-week treatment period (92%). Compliance rates did not differ by group assignment. Four-

week quit rates (verified with CO) were 82% for the mCM and 45% for the yoked controls. Three-month self-report quit rates were 50% in the mCM and 18% in the yoked controls. mCM may be a useful adjunctive smoking cessation treatment component for reducing smoking among smokers with PTSD, particularly early in a smoking quit attempt.

### **Smokers Versus Snorters: Do Treatment Outcomes Differ According to Route of Cocaine**

**Administration** Kiluk BD, Babuscio TA, Nich C, Carroll KM. Exp Clin Psychopharmacol. 2013 Dec; 21(6): 490-498.

Smoking cocaine achieves maximal concentration and effect far more rapidly than through the intranasal ("snorting") route, and it is associated with greater propensity for dependence and more severe consequences. However, very little is known about differences in treatment outcome according to route of administration. This study compared treatment outcomes, such as frequency of cocaine use and Addiction Severity Index (ASI) composite scores, by primary route of cocaine administration (smoking vs. intranasal) among a pooled sample of 412 cocaine-dependent individuals participating in 1 of 5 randomized clinical trials. The majority (80%) reported smoking as their primary route of cocaine administration. Overall, results indicated better cocaine use outcomes both during the treatment phase and through a 12-month follow-up period for intranasal users compared to smokers, although not all differences reached statistical significance. Intranasal users remained in treatment longer,  $F(1, 408) = 3.55$ ,  $p < .05$ , and showed a trend toward achieving longer periods of sustained abstinence within treatment,  $F(1, 378) = 2.68$ ,  $p = .08$ , as well as less use over time during the follow-up period than smokers (Time  $\times$  Route:  $t = 1.87$ ,  $p = .06$ ). Also, intranasal users' ASI cocaine composite score decreased more than smokers, but there were overall decreases in the other ASI domains for all participants over the course of the study period. These results suggest that intranasal users may achieve better cocaine use outcomes than smokers, yet this doesn't appear to translate to differential changes in the severity of problems experienced in other life areas.

### **Real-time fMRI Links Subjective Experience with Brain Activity during Focused Attention**

Garrison KA1, Scheinost D, Worhunsky PD, Elwafi HM, Thornhill TA 4th, Thompson E, Saron C, Desbordes G, Kober H, Hampson M, Gray JR, Constable RT, Papademetris X, Brewer JA. Neuroimage. 2013 Nov 1; 81: 110-118.

Recent advances in brain imaging have improved the measure of neural processes related to perceptual, cognitive and affective functions, yet the relation between brain activity and subjective experience remains poorly characterized. In part, it is a challenge to obtain reliable accounts of participant's experience in such studies. Here the authors addressed this limitation by utilizing experienced meditators who are expert in introspection. They tested a novel method to link objective and subjective data, using real-time fMRI (rt-fMRI) to provide participants with feedback of their own brain activity during an ongoing task. They provided real-time feedback during a focused attention task from the posterior cingulate cortex, a hub of the default mode network shown to be activated during mind-wandering and deactivated during meditation. In a first experiment, both meditators and non-meditators reported significant correspondence between the feedback graph and their subjective experience of focused attention and mind-wandering. When instructed to volitionally decrease the feedback graph, meditators, but not non-meditators, showed significant deactivation of the posterior cingulate cortex. The authors were able to replicate these results in a separate group of meditators using a novel step-wise rt-fMRI discovery protocol in which participants were not provided with prior knowledge of the expected relationship between their experience and the feedback graph (i.e., focused attention versus mind-wandering). These findings support the feasibility of using rt-fMRI to link objective measures of brain activity with reports of ongoing subjective experience in cognitive

neuroscience research, and demonstrate the generalization of expertise in introspective awareness to novel contexts.

**A Preliminary Investigation of Stroop-related Intrinsic Connectivity in Cocaine Dependence: Associations with Treatment Outcomes** Mitchell MR, Balodis IM, Devito EE, Lacadie CM, Yeston J, Scheinost D, Constable RT, Carroll KM, Potenza MN. Am J Drug Alcohol Abuse. 2013 Nov; 39(6): 392-402.

Cocaine-dependent individuals demonstrate neural and behavioral differences compared to healthy comparison subjects when performing the Stroop color-word interference test. Stroop measures also relate to treatment outcome for cocaine dependence. Intrinsic connectivity analyses assess the extent to which task-related regional brain activations are related to each other in the absence of defining a priori regions of interest. This study examined 1) the extent to which cocaine-dependent and non-addicted individuals differed on measures of intrinsic connectivity during fMRI Stroop performance; and 2) the relationships between fMRI Stroop intrinsic connectivity and treatment outcome in cocaine dependence. Sixteen treatment-seeking cocaine-dependent patients and matched non-addicted comparison subjects completed an fMRI Stroop task. Between-group differences in intrinsic connectivity were assessed and related to self-reported and urine-toxicology-based cocaine-abstinence measures. Cocaine-dependent patients vs. comparison subjects showed less intrinsic connectivity in cortical and subcortical regions. When adjusting for individual degree of intrinsic connectivity, cocaine-dependent vs. comparison subjects showed relatively greater intrinsic connectivity in the ventral striatum, putamen, inferior frontal gyrus, anterior insula, thalamus and substantia nigra. Non-mean-adjusted intrinsic-connectivity measures in the midbrain, thalamus, ventral striatum, substantia nigra, insula and hippocampus negatively correlated with measures of cocaine abstinence. The diminished intrinsic connectivity in cocaine-dependent vs. comparison subjects suggests poorer communication across brain regions during cognitive-control processes. In mean-adjusted analyses, the cocaine-dependent group displayed relatively greater Stroop-related connectivity in regions implicated in motivational processes in addictions. The relationships between treatment outcomes and connectivity in the midbrain and basal ganglia suggest that connectivity represents a potential treatment target.

**Development and Preliminary Randomized Controlled Trial of a Distress Tolerance Treatment for Smokers with a History of Early Lapse** Brown RA, Reed KM, Bloom EL, Minami H, Strong DR, Lejuez CW, Kahler CW, Zvolensky MJ, Gifford EV, Hayes SC. Nicotine Tob Res. 2013 Dec; 15(12): 2005-2015.

An inability to tolerate distress is a significant predictor of early smoking lapse following a cessation attempt. The authors conducted a preliminary randomized controlled trial to compare a distress tolerance (DT) treatment that incorporated elements of exposure-based therapies and Acceptance and Commitment Therapy to standard smoking cessation treatment (ST). Smokers with a history of early lapse in prior quit attempts received either DT (N = 27; 9 2-hr group and 6 50-min individual sessions) or ST (N = 22; 6 90-min group and 1 20-min individual session), plus 8 weeks of transdermal nicotine patch. At the end of behavioral treatment, odds of abstinence among participants receiving DT were 6.46 times greater than among participants receiving ST (66.7% vs. 31.8%), equivalent to a medium-to large-effect size. Odds of abstinence for DT were still 1.73 times greater at 8 weeks, corresponding to a small- to medium-effect size, although neither this difference nor those at 13 and 26 weeks were statistically significant. Furthermore, of those who lapsed to smoking during the first week postquit, DT participants had more than 4 times greater odds of abstinence than ST participants at the end of treatment. Relative to ST, DT participants also reported a larger decrease in experiential avoidance, a hypothesized DT treatment mediator, prior to quit day. The trajectory of negative mood and



withdrawal symptoms in DT differed from ST and was largely consistent with hypotheses. Reasons for the decrease in abstinence in DT after treatment discontinuation and suggestions for future research are discussed.

### **Efficacy of Dual Focus Mutual Aid for Persons with Mental Illness and Substance Misuse**

Rosenblum A, Matusow H, Fong C, Vogel H, Uttaro T, Moore TL, Magura S. *Drug Alcohol Depend.* 2014 Feb 1; 135: 78-87.

Previous studies have indicated that persons with co-occurring mental health and substance use problems can benefit by attending dual-focus mutual aid groups. However, to date, a trial to test the efficacy of these groups has not been published. This study randomly assigned 203 substance misusing clients attending a mental health or dual-diagnosis facility to either a dual-focus 12-step group (Double Trouble in Recovery; DTR) or a waiting list control group. Participants were followed for 3-6 months. The primary outcome was substance use (days used in the past 30 with saliva testing to detect under-reporting); secondary outcomes included psychiatric medication adherence, attendance at traditional (single-focus) 12-step meetings (e.g., AA/NA); and improvement in mental health and substance use problems (quality of life). Multilevel model (MLM) regression was used to analyze the nested effect of participants within 8 facilities (7 in New York City and 1 in Michigan). Regression imputation was used to adjust for drug use under-reporting. At follow-up 79% of the subjects were interviewed. In intent to treat analysis, DTR subjects compared with control subjects used alcohol ( $p=.03$ ) and any substances ( $p=.02$ ) on fewer days. DTR compared with control subjects were also more likely to rate themselves as experiencing better mental health and fewer substance use problems ( $p=.001$ ). There were no effects for DTR on drug use only, medication adherence or NA/AA attendance. Findings reported in previous studies on the association between exposure to DTR and reductions in substance use were partially supported in this efficacy trial.

### **A Randomized, Double-blind Evaluation of Buprenorphine Taper Duration in Primary Prescription Opioid Abusers**

Sigmon SC, Dunn KE, Saulsgiver K, Patrick ME, Badger GJ, Heil SH, Brooklyn JR, Higgins ST. *JAMA Psychiatry.* 2013 Dec; 70(12): 1347-1354.

The objective of this study was to evaluate, following brief stabilization with a combination of buprenorphine hydrochloride and naloxone hydrochloride dihydrate, the relative efficacy of 1-, 2-, and 4-week buprenorphine tapering regimens and subsequent naltrexone hydrochloride therapy in PO-dependent outpatients. A double-blind, 12-week randomized clinical trial was conducted in an outpatient research clinic. Following a brief period of buprenorphine stabilization, 70 PO-dependent adults were randomized to receive 1-, 2-, or 4-week tapers followed by naltrexone therapy. During phase 1 (weeks 1-5 after randomization), participants visited the clinic daily; during phase 2 (weeks 6-12), visits were reduced to thrice weekly. Participants received behavioral therapy and urine toxicology testing throughout the trial. Main outcomes and measures included the percentage of participants negative for illicit opioid use, retention, naltrexone ingestion, and favorable treatment response (i.e., retained in treatment, opioid abstinent, and receiving naltrexone at the end of the study). Opioid abstinence at the end of phase 1 was greater in the 4-week compared with the 2- and 1-week taper conditions ( $P = .02$ ), with 63% ( $n = 14$ ), 29% ( $n = 7$ ), and 29% ( $n = 7$ ) of participants abstinent in the 4-, 2-, and 1-week conditions, respectively. Abstinence at the end of phase 2 was also greater in the 4-week compared with the 2- and 1-week conditions ( $P = .03$ ), with 50% ( $n = 11$ ), 16% ( $n = 4$ ), and 20% ( $n = 5$ ) of participants abstinent in the 4-, 2-, and 1-week conditions, respectively. There were more treatment responders in the 4-week condition ( $P = .03$ ), with 50% ( $n = 11$ ), 17% ( $n = 4$ ), and 21% ( $n = 5$ ) of participants in the 4-, 2-, and 1-week groups considered responders at the end of treatment, respectively. Retention and naltrexone ingestion also were superior in the 4-week vs briefer tapers (both  $P = .04$ ). Experimental condition (i.e., taper duration) was the strongest predictor of treatment

response, followed by buprenorphine stabilization dose. This study represents a rigorous experimental evaluation of outpatient buprenorphine stabilization, brief taper, and naltrexone maintenance for treatment of PO dependence. Results suggest that a meaningful subset of PO-dependent outpatients may respond positively to a 4-week taper plus naltrexone maintenance intervention.

**Commitment Strength, Alcohol Dependence and HealthCall Participation: Effects on Drinking Reduction in HIV Patients** Aharonovich E, Stohl M, Ellis J, Amrhein P, Hasin D. *Drug Alcohol Depend.* 2014 Feb 1; 135: 112-118.

The role of three factors in drinking outcome after brief intervention among heavily drinking HIV patients were investigated: strength of commitment to change drinking, alcohol dependence, and treatment type: brief Motivational Interview (MI) only, or MI plus HealthCall, a technological extension of brief intervention. HIV primary care patients (N=139) who drank  $\geq 4$  drinks at least once in the 30 days before study entry participated in MI-only or MI+HealthCall in a randomized trial to reduce drinking. Patients were 95.0% minority; 23.0% female; 46.8% alcohol dependent; mean age 46.3. Outcome at end of treatment (60 days) was drinks per drinking day (Timeline Follow-Back). Commitment strength (CS) was rated from MI session recordings. Overall, stronger CS predicted end-of-treatment drinking ( $p < .001$ ). After finding an interaction of treatment, CS and alcohol dependence ( $p = .01$ ), the authors examined treatment $\times$ CS interactions in alcohol dependent and non-dependent patients. In alcohol dependent patients, the treatment $\times$ commitment strength interaction was significant ( $p = .006$ ); patients with low commitment strength had better outcomes in MI+HealthCall than in MI-only (lower mean drinks per drinking day; 3.5 and 4.6 drinks, respectively). In non-dependent patients, neither treatment nor CS predicted outcome. Among alcohol dependent HIV patients, HealthCall was most beneficial in drinking reduction when MI ended with low commitment strength. HealthCall may not merely extend MI effects, but add effects of its own that compensate for low commitment strength. Thus, HealthCall may also be effective when paired with briefer interventions requiring less skill, training and supervision than MI. Replication is warranted.

**Computerized Versus In-person Brief Intervention for Drug Misuse: A Randomized Clinical Trial** Schwartz RP, Gryczynski J, Mitchell SG, Gonzales A, Moseley A, Peterson TR, Ondersma SJ, O'Grady KE. *Addiction.* 2014 Feb 12. doi: 10.1111/add.12502. [Epub ahead of print].

Several studies have found that brief interventions (BIs) for drug misuse have superior effectiveness to no-treatment controls. However, many health centers do not provide BIs for drug use consistently due to insufficient behavioral health staff capacity. Computerized BIs for drug use are a promising approach, but their effectiveness compared with in-person BIs has not been established. This study compared the effectiveness of a computerized brief intervention (CBI) to an in-person brief intervention (IBI) delivered by a behavioral health counselor. This was a two-arm randomized clinical trial, conducted in two health centers in New Mexico, United States. Participants were 360 adult primary care patients with moderate-risk drug scores on the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) who were randomly assigned on a 1 : 1 basis to a computerized brief intervention (CBI) or to an in-person brief intervention (IBI) delivered by a behavioral health counselor. Assessments were conducted at baseline and 3-month follow-up, and included the ASSIST and drug testing on hair samples. The IBI and CBI conditions did not differ at 3 months on global ASSIST drug scores [ $b = -1.79$ ; 95% confidence interval (CI) = -4.37, 0.80] or drug-positive hair tests [odds ratio (OR) = 0.97; 95% CI = 0.47, 2.02]. There was a statistically significant advantage of CBI over IBI in substance-specific ASSIST scores for marijuana ( $b = -1.73$ ; 95% CI = -2.91, -0.55; Cohen's  $d = 0.26$ ;  $P = 0.004$ ) and cocaine ( $b = -4.48$ ; 95% CI = -8.26, -0.71; Cohen's  $d = 0.50$ ;  $P = 0.021$ ) at 3

months. Computerized brief intervention can be an effective alternative to in-person brief intervention for addressing moderate drug use in primary care.

**Toward Empirical Identification of a Clinically Meaningful Indicator of Treatment Outcome: Features of Candidate Indicators and Evaluation of Sensitivity to Treatment Effects and Relationship to One Year Follow Up Cocaine Use Outcomes**

Carol KM, Kiluk, BD, Nich C, DeVito EE, Decker S, LaPaglia D, Duffey D, Babuscio TA, Ball SA. Drug and Alcohol Dependence. 2014 Apr; 137C: 3-19.

Selection of an appropriate indicator of treatment response in clinical trials is complex, particularly for the various illicit drugs of abuse. Most widely used indicators have been selected based on expert group recommendation or convention rather than systematic empirical evaluation. Absence of an evidence-based, clinically meaningful index of treatment outcome hinders cross-study evaluations necessary for progress in addiction treatment science. Fifteen candidate indicators used in multiple clinical trials as well as some proposed recently are identified and discussed in terms of relative strengths and weaknesses (practicality, cost, verifiability, sensitivity to missing data). Using pooled data from five randomized controlled trials of cocaine dependence (N=434), the indicators were compared in terms of sensitivity to the effects of treatment and relationship to cocaine use and general functioning during follow-up. Commonly used outcome measures (percent negative urine screens; percent days of abstinence) performed relatively well in that they were sensitive to the effects of the therapies evaluated. Others, including complete abstinence and reduction in frequency of use, were less sensitive to effects of specific therapies and were very weakly related to cocaine use or functioning during follow-up. Indicators more strongly related to cocaine use during follow-up were those that reflected achievement of sustained periods of abstinence, particularly at the end of treatment. These analyses did not demonstrate overwhelming superiority of any single indicator, but did identify several that performed particularly poorly. Candidates for elimination included retention, complete abstinence, and indicators of reduced frequency of cocaine use.

## **RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE**

**Acute and Chronic Effects Of the M1/M4-Preferring Muscarinic Agonist Xanomeline On Cocaine Vs. Food Choice In Rats** Thomsen M, Fulton BS, Caine SB. Psychopharmacology (Berl). 2014 Feb; 231(3): 469-479.

The authors previously showed that the M1/M4-preferring muscarinic agonist xanomeline can acutely attenuate or eliminate cocaine self-administration in mice. Medications used to treat addictions will arguably be administered in (sub)chronic or repeated regimens. Tests of acute effects often fail to predict chronic effects, highlighting the need for chronic testing of candidate medications. Rats were trained to lever press under a concurrent FR5 FR5 schedule of intravenous cocaine and food reinforcement. Once baseline behavior stabilized, the effects of 7 days once-daily injections of xanomeline were evaluated. Xanomeline pretreatment dose-dependently (1. 8-10 mg/kg/day) shifted the dose-effect curve for cocaine rightward (up to 5. 6-fold increase in A 50), with reallocation of behavior to the food-reinforced lever. There was no indication of tolerance, rather effects grew over days. The suppression of cocaine choice appeared surmountable at high cocaine doses, and xanomeline treatment did not significantly decrease total-session cocaine or food intake. In terms of xanomeline's potential for promoting abstinence from cocaine in humans, the findings were mixed. Xanomeline did produce reallocation of behavior from cocaine to food with a robust increase in food reinforcers earned at some cocaine/xanomeline dose combinations. However, effects appeared surmountable, and food-maintained behavior was also decreased at some xanomeline/cocaine dose combinations, suggesting clinical usefulness may be limited. These data nevertheless support the notion that chronic muscarinic receptor stimulation can reduce cocaine self-administration. Future studies should show whether ligands with higher selectivity for M1 or M1/M4 subtypes would be less limited by undesired effects and can achieve higher efficacy.

**Effects Of Chronic Varenicline Treatment On Nicotine, Cocaine, and Concurrent Nicotine+ Cocaine Self-Administration** Mello NK, Fivel PA, Kohut SJ, Carroll FI. Neuropsychopharmacology. 2014 Apr; 39(5): 1222-1231.

Nicotine dependence and cocaine abuse are major public health problems, and most cocaine abusers also smoke cigarettes. An ideal treatment medication would reduce both cigarette smoking and cocaine abuse. Varenicline is a clinically available, partial agonist at  $\alpha 4\beta 2^*$  and  $\alpha 6\beta 2^*$  nicotinic acetylcholine receptors (nAChRs) and a full agonist at  $\alpha 7$  nAChRs. Varenicline facilitates smoking cessation in clinical studies and reduced nicotine self-administration, and substituted for the nicotine-discriminative stimulus in preclinical studies. The present study examined the effects of chronic varenicline treatment on self-administration of IV nicotine, IV cocaine, IV nicotine+cocaine combinations, and concurrent food-maintained responding by five cocaine- and nicotine-experienced adult rhesus monkeys (*Macaca mulatta*). Varenicline (0. 004-0. 04mg/kg/h) was administered intravenously every 20min for 23h each day for 7-10 consecutive days. Each varenicline treatment was followed by saline-control treatment until food- and drug-maintained responding returned to baseline. During control treatment, nicotine+cocaine combinations maintained significantly higher levels of drug self-administration than nicotine or cocaine alone ( $P < 0. 05$ -0. 001). Varenicline dose-dependently reduced responding maintained by nicotine alone (0. 0032mg/kg/inj) ( $P < 0. 05$ ), and in combination with cocaine (0. 0032mg/kg/inj) ( $P < 0. 05$ ) with no significant effects on food-maintained responding. However, varenicline did not significantly decrease self-administration of a low dose of nicotine (0. 001mg/kg), cocaine alone (0. 0032 and 0. 01mg/kg/inj), or 0. 01mg/kg cocaine combined with the same doses of nicotine. The authors conclude that varenicline selectively attenuates the reinforcing effects of nicotine alone but not cocaine alone, and its effects on nicotine+cocaine combinations are dependent on the

dose of cocaine.

**The Cannabinoid Agonist HU-210: Pseudo-Irreversible Discriminative Stimulus Effects In Rhesus Monkeys** Hrubá L, McMahon LR. Eur J Pharmacol. 2014 Mar; 727 [Epub ahead of print] 35-42.

Synthetic cannabinoid abuse and case reports of adverse effects have raised concerns about the pharmacologic mechanisms underlying in vivo effects. Here, a synthetic cannabinoid identified in abused products (HU-210) was compared to the effects of  $\Delta(9)$ -THC and two other synthetic cannabinoid agonists used extensively in pre-clinical studies (CP 55,940 and WIN 55,212-2). One group of monkeys discriminated  $\Delta(9)$ -THC (0.1mg/kg i.v.); a separate group received chronic  $\Delta(9)$ -THC (1mg/kg/12h s.c.) and discriminated rimonabant (1mg/kg i.v.). CP 55,940, HU-210,  $\Delta(9)$ -THC, and WIN 55,212-2 produced  $\Delta(9)$ -THC lever responding. HU-210 had a long duration (i.e., 1-2 days), whereas that of the other cannabinoids was 5h or less. Rimobabant (1mg/kg) produced surmountable antagonism; single dose-apparent affinity estimates determined in the presence of  $\Delta(9)$ -THC, CP 55,940, and WIN 55,212-2 did not differ from each other. In contrast, rimobabant (1mg/kg) produced a smaller rightward shift in the HU-210 dose-effect function. In  $\Delta(9)$ -THC treated monkeys, the relative potency of CP 55,940,  $\Delta(9)$ -THC, and WIN 55,212-2 to attenuate the discriminative stimulus effects of rimobabant was the same as that evidenced in the  $\Delta(9)$ -THC discrimination, whereas HU-210 was unexpectedly more potent in attenuating the effects of rimobabant. In conclusion, the same receptor subtype mediates the discriminative stimulus effects of  $\Delta(9)$ -THC, CP 55,940 and WIN 55,212-2. The limited effectiveness of rimobabant to either prevent or reverse the effects of HU-210 appears to be due to very slow dissociation or pseudo-irreversible binding of HU-210 at cannabinoid receptors.

**Nicotine-Like Behavioral Effects Of the Minor Tobacco Alkaloids Nornicotine, Anabasine, and Anatabine In Male Rodents** Caine SB, Collins GT, Thomsen M, Wright C, Lanier RK, Mello NK. Exp Clin Psychopharmacol. 2014 Feb; 22(1): 41904.

Tobacco use is associated with lethal diseases in an estimated 440,000 persons in the United States each year. Successful smoking quit-rates are estimated at 5%-8%, even though a quarter of those attempts included use of smoking-cessation aids. Current projections are that 16% of the U. S. population- 35 million people- will still smoke in 2025, thus more effective smoking-cessation aids are urgently needed. The minor tobacco alkaloids may be promising candidates, but further research is necessary. Accordingly, the authors systematically evaluated the minor tobacco alkaloids nornicotine, anabasine, and anatabine using assays of behavioral tolerability, nicotine withdrawal, nicotine discrimination, and nicotine self-administration in male rodents. At doses that were well tolerated, all 3 minor alkaloids dose-dependently engendered robust substitution for a nicotine discriminative stimulus in mice (0.32 mg/kg, IP), and anabasine attenuated nicotine withdrawal. When the ED<sub>50</sub> dose of each alkaloid was administered in combination with nicotine, the discriminative stimulus effects of nicotine were not enhanced by any of the alkaloids, and anatabine blunted nicotine's effects. In drug self-administration studies, only nornicotine was self-administered by rats that self-administered nicotine intravenously; anabasine and anatabine had no reinforcing effects. Moreover, prior administration of each of the minor tobacco alkaloids dose-dependently decreased nicotine self-administration. Collectively these results suggest that the minor tobacco alkaloids may substitute for the subjective effects of nicotine and attenuate withdrawal and craving without the abuse liability of nicotine.

### **Injection Route and TLR9 Agonist Addition Significantly Impact Heroin Vaccine Efficacy**

Bremer PT, Schlosburg JE, Lively JM, Janda KD. Mol Pharm. 2014 Feb; [Epub ahead of print].

Active immunization is an effective means of blocking the pharmacodynamic effects of drugs and holds promise as a treatment for heroin addiction. Previously, the authors demonstrated the efficacy of their first-generation vaccine in blocking heroin self-administration in rats, however, many vaccine components can be modified to further improve performance. Herein they examine the effects of varying heroin vaccine injection route and adjuvant formulation. Mice immunized via subcutaneous (s.c.) injection exhibited inferior anti-heroin titers compared to intraperitoneal (i. p.) and s. c. /i. p. co-administration injection routes. Addition of TLR9 agonist cytosine-guanine oligodeoxynucleotide 1826 (CpG ODN 1826) to the original alum adjuvant elicited superior antibody titers and opioid affinities compared to alum alone. To thoroughly assess vaccine efficacy, full dose-response curves were generated for heroin-induced analgesia in both hot plate and tail immersion tests. Mice treated with CpG ODN 1826 exhibited greatly shifted dose-response curves (10-13 fold vs. unvaccinated controls) while non-CpG ODN vaccine groups did not exhibit the same robust effect (2-7 fold shift for i. p. and combo, 2-3 fold shift for s.c ). These results suggest CpG ODN 1826 is a highly potent adjuvant, and injection routes should be considered for development of small molecule-protein conjugate vaccines. Lastly, this study has established a new standard for assessing drugs of abuse vaccines, wherein a full dose-response curve should be performed in an appropriate behavioral task.

### **Preclinical Characterization Of An Anti-Methamphetamine Monoclonal Antibody For Human Use**

Stevens MW, Tawney RL, West CM, Kight AD, Henry RL, Owens SM, Gentry WB. MABs. 2014 Mar; 6(2): 547-555.

Ch-mAb7F9, a human-mouse chimeric monoclonal antibody (mAb) designed to bind (+)-methamphetamine (METH) with high affinity and specificity, was produced as a treatment medication for METH abuse. In these studies, the authors present the preclinical characterization that provided predictive evidence that ch-mAb7F9 may be safe and effective in humans. In vitro ligand binding studies showed that ch-mAb7F9 is specific for and only binds its target ligands (METH, (+)-amphetamine, and 3,4-methylenedioxy-N-methylamphetamine) with high affinity. It did not bind endogenous neurotransmitters or other medications and was not bound by protein C1q, thus it is unlikely to stimulate in vivo complement-dependent cytotoxicity. Isothermal titration calorimetry potency studies showed that METH binding by ch-mAb7F9 is efficient. Pharmacokinetic studies of METH given after ch-mAb7F9 doses in rats demonstrated the in vivo application of these in vitro METH-binding characteristics. While METH had little effect on ch-mAb7F9 disposition, ch-mAb7F9 substantially altered METH disposition, dramatically reducing the volume of distribution and clearance of METH. The elimination half-life of METH was increased by ch-mAb7F9, but it was still very fast compared with the elimination of ch-mAb7F9. Importantly, the rapid elimination of unbound METH combined with previous knowledge of mAb:target ligand binding dynamics suggested that ch-mAb7F9 binding capacity regenerates over time. This finding has substantial therapeutic implications regarding the METH doses against which ch-mAb7F9 will be effective, on the duration of ch-mAb7F9 effects, and on the safety of ch-mAb7F9 in METH users who use METH while taking ch-mAb7F9. These results helped to support initiation of a Phase 1a study of ch-mAb7F9.

### **Affinity Improvement Of A Therapeutic Antibody To Methamphetamine and Amphetamine Through Structure-Based Antibody Engineering**

Thakkar S, Nanaware-Kharade N, Celikel R, Peterson EC, Varughese KI. Sci Rep. 2014; 4[Epub ahead of print] 3673.

Methamphetamine (METH) abuse is a worldwide threat, without any FDA approved medications. Anti-METH IgGs and single chain fragments (scFvs) have shown efficacy in preclinical studies. Here the authors report affinity enhancement of an anti-METH scFv for METH and its active metabolite

amphetamine (AMP), through the introduction of point mutations, rationally designed to optimize the shape and hydrophobicity of the antibody binding pocket. The binding affinity was measured using saturation binding technique. The mutant scFv-S93T showed 3.1 fold enhancement in affinity for METH and 26 fold for AMP. The scFv-I37M and scFv-Y34M mutants showed enhancement of 94, and 8 fold for AMP, respectively. Structural analysis of scFv-S93T:METH revealed that the substitution of Ser residue by Thr caused the expulsion of a water molecule from the cavity, creating a more hydrophobic environment for the binding that dramatically increases the affinities for METH and AMP.

**Structural Characterization Of A Therapeutic Anti-Methamphetamine Antibody Fragment: Oligomerization and Binding Of Active Metabolites**

Peterson EC, Celikel R, Gokulan K, Varughese KI. PLoS One. 2013; 8(12): e82690.

Vaccines and monoclonal antibodies (mAb) for treatment of (+)-methamphetamine (METH) abuse are in late stage preclinical and early clinical trial phases, respectively. These immunotherapies work as pharmacokinetic antagonists, sequestering METH and its metabolites away from sites of action in the brain and reduce the rewarding and toxic effects of the drug. A key aspect of these immunotherapy strategies is the understanding of the subtle molecular interactions important for generating antibodies with high affinity and specificity for METH. The authors previously determined crystal structures of a high affinity anti-METH therapeutic single chain antibody fragment (scFv6H4, K(D) = 10 nM) in complex with METH and the (+) stereoisomer of 3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy"). Here they report the crystal structure of scFv6H4 in homo-trimeric unbound (apo) form (2.60 Å), as well as monomeric forms in complex with two active metabolites; (+)-amphetamine (AMP, 2.38 Å) and (+)-4-hydroxy methamphetamine (p-OH-METH, 2.33 Å). The apo structure forms a trimer in the crystal lattice and it results in the formation of an intermolecular composite beta-sheet with a three-fold symmetry. The authors were also able to structurally characterize the coordination of the His-tags with Ni(2+). Two of the histidine residues of each C-terminal His-tag interact with Ni(2+) in an octahedral geometry. In the apo state the CDR loops of scFv6H4 form an open conformation of the binding pocket. Upon ligand binding, the CDR loops adopt a closed formation, encasing the drug almost completely. The structural information reported here elucidates key molecular interactions important in anti-methamphetamine abuse immunotherapy.

**Maintained Cocaine Self-Administration Is Determined By Quantal Responses: Implications For the Measurement Of Antagonist Potency**

Norman AB, Tabet MR, Norman MK, Tsibulsky VL. J Pharmacol Exp Ther. 2014 Feb; 348(2): 311-315.

The change in frequency of cocaine self-administration as a function of the unit dose is widely assumed to represent a graded pharmacodynamic response. Alternatively, a pharmacological theory states that during maintained self-administration, a quantal response occurs at a minimum maintained cocaine concentration (satiety threshold). Rats self-administered cocaine at unit doses spanning an 8-fold range from 0.75 to 6 µmol/kg. Despite an approximately 7-fold difference in the interinjection intervals, there were no differences in the plasma cocaine concentration at the time of lever press across this range of unit doses, consistent with the satiety threshold representing an equiactive cocaine concentration. Because self-administration always occurs when cocaine concentrations decline back to the satiety threshold, this behavior represents a process of automatic back titration of equiactive agonist concentrations. Therefore, the lower frequency of self-administration at higher unit doses is caused by an increase in the duration of the cocaine-induced satiety response, and the graded dose-frequency relationship is due to cocaine pharmacokinetics. After the interinjection intervals at a particular unit dose were stable, rats were injected with the competitive D<sub>1</sub>-like dopamine receptor antagonist R-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine

(SCH23390; 15 nmol/kg intravenously) and the session continued. At all cocaine unit doses, SCH23390 accelerated self-administration with a concomitant increase in the calculated satiety threshold, and these equiactive cocaine concentration ratios were independent of the cocaine unit dose. Therefore, the measurement of antagonist potency requires only a single unit dose of cocaine, selected on the basis of convenience, and using multiple cocaine unit doses is redundant.

**Probing the Effects Of Hapten Stability On Cocaine Vaccine Immunogenicity** Cai X, Whitfield T, Moreno AY, Grant Y, Hixon MS, Koob GF, Janda KD. Mol Pharm. 2013 Nov; 10(11): 4176-4184. Judicious hapten design has been shown to be of importance when trying to generate a viable vaccine against a drug of abuse. Hapten design has typically been predicated upon faithfully emulating the unique chemical architecture that each drug presents. However, the need for drug-hapten congruency may also compromise vaccine immunogenicity if the drug-hapten conjugate possesses chemical epitope instability. There has been no systematic study on the impact of hapten stability as it relates to vaccine immunogenicity. As a starting point, the authors have probed the stability of a series of cocaine haptens through varying several of its structural elements, including functionality at the C2-position, the nature of the linker, and its site of attachment. Accordingly, a hydrolytic stability profile of four cocaine haptens (GNNA, GNNS, GNE, and GNC) was produced, and these results were compared through each hapten's immunological properties, which were generated via active vaccination. From this group of four, three of the haptens, GNE, GNNA, and GNC, were further examined in an animal behavioral model, and findings here were again measured in relationship to hapten stability. The authors demonstrate a corresponding relationship between the half-life of the hapten and its immunogenicity, wherein haptens presenting a fully representative cocaine framework elicited higher concentrations of cocaine-specific IgG in sera and also conferred better protection against cocaine-induced locomotor activity. These results indicate that hapten half-life plays an important role in vaccine immunogenicity and this in turn can impact animal behavioral effects when challenged with a drug of abuse.

**Neuroprotective Targets Through Which 6-Acetyl-3-(4-(4-(4-Fluorophenyl)Piperazin-1-yl)Butyl)Benzo[D]Oxazol-2(3H)-One (Sn79), A Sigma Receptor Ligand, Mitigates The Effects Of Methamphetamine In Vitro** Kaushal N, Robson MJ, Rosen A, McCurdy CR, Matsumoto RR. Eur J Pharmacol. 2014 Feb; 724[Epub ahead of print] 193-203.

Exposure to high or repeated doses of methamphetamine can cause hyperthermia and neurotoxicity, which are thought to increase the risk of developing a variety of neurological conditions. Sigma receptor antagonism can prevent methamphetamine-induced hyperthermia and neurotoxicity, but the underlying cellular targets through which the neuroprotection is conveyed remain unknown. Differentiated NG108-15 cells were thus used as a model system to begin elucidating the neuroprotective mechanisms targeted by sigma receptor antagonists to mitigate the effects of methamphetamine. In differentiated NG108-15 cells, methamphetamine caused the generation of reactive oxygen/nitrogen species, an increase in PERK-mediated endoplasmic reticulum stress and the activation of caspase-3, -8 and -9, ultimately resulting in apoptosis at micromolar concentrations, and necrotic cell death at higher concentrations. The sigma receptor antagonist, 6-acetyl-3-(4-(4-(4-fluorophenyl)piperazin-1-yl)butyl)benzo[d]oxazol-2(3H)-one (SN79), attenuated methamphetamine-induced increases in reactive oxygen/nitrogen species, activation of caspase-3, -8 and -9 and accompanying cellular toxicity. In contrast, 1,3-di(2-tolyl)-guanidine (DTG), a sigma receptor agonist, shifted the dose response curve of methamphetamine-induced cell death towards the left. To probe the effect of temperature on neurotoxicity, NG108-15 cells maintained at an elevated temperature (40°C) exhibited a significant and synergistic increase in cell death in response to methamphetamine, compared to cells maintained at a normal cell culture temperature (37°C). SN79 attenuated the



enhanced cell death observed in the methamphetamine-treated cells at 40°C. Together, the data demonstrate that SN79 reduces methamphetamine-induced reactive oxygen/nitrogen species generation and caspase activation, thereby conveying neuroprotective effects against methamphetamine under regular and elevated temperature conditions.

**Controlled-Deactivation Cannabinergic Ligands** Sharma R, Nikas SP, Paronis CA, Wood JT, Halikhedkar A, Guo JJ, Thakur GA, Kulkarni S, Benchama O, Raghav JG, Gifford RS, Järbe TU, Bergman J, Makriyannis A. *J Med Chem.* 2013 Dec; 56(24): 10142-10157.

The authors report an approach for obtaining novel cannabinoid analogues with controllable deactivation and improved druggability. Their design involves the incorporation of a metabolically labile ester group at the 2'-position on a series of (-)- $\Delta(8)$ -THC analogues. The authors have sought to introduce benzylic substituents  $\alpha$  to the ester group which affect the half-lives of deactivation through enzymatic activity while enhancing the affinities and efficacies of individual ligands for the CB1 and CB2 receptors. The 1'-(S)-methyl, 1'-gem-dimethyl, and 1'-cyclobutyl analogues exhibit remarkably high affinities for both CB receptors. The novel ligands are susceptible to enzymatic hydrolysis by plasma esterases in a controllable manner, while their metabolites are inactive at the CB receptors. In further in vitro and in vivo experiments key analogues were shown to be potent CB1 receptor agonists and to exhibit CB1-mediated hypothermic and analgesic effects.

**[<sup>125</sup>I]AT-1012, A New High Affinity Radioligand For The  $\alpha 3\beta 4$  Nicotinic Acetylcholine Receptors** Wu J, Perry DC, Bupp JE, Jiang F, Polgar WE, Toll L, Zaveri NT. *Neuropharmacology.* 2014 Feb; 77[Epub ahead of print] 193-199.

Recent genetic and pharmacological studies have implicated the  $\alpha 3$ ,  $\beta 4$  and  $\alpha 5$  subunits of the nicotinic acetylcholine receptor (nAChR) in dependence to nicotine and other abused drugs and nicotine withdrawal. The  $\alpha 3\beta 4^*$  nAChR subtype has been shown to co-assemble with the  $\alpha 5$  or  $\beta 3$  nAChR subunits, and is found mainly in the autonomic ganglia and select brain regions. It has been difficult to study the  $\alpha 3\beta 4$  nAChR because there have been no selective nonpeptidic ligands available to independently examine its pharmacology. The authors recently reported the synthesis of a [<sup>125</sup>I]-radiolabeled analog of a high affinity, selective small-molecule  $\alpha 3\beta 4$  nAChR ligand, AT-1012. The authors report here the vitro characterization of this radioligand in receptor binding and in vitro autoradiographic studies targeting the  $\alpha 3\beta 4^*$  nAChR. Binding of [<sup>125</sup>I]AT-1012 was characterized at the rat  $\alpha 3\beta 4$  and  $\alpha 4\beta 2$  nAChR transfected into HEK cells, as well as at the human  $\alpha 3\beta 4\alpha 5$  nAChR in HEK cells. Binding affinity of [<sup>125</sup>I]AT-1012 at the rat  $\alpha 3\beta 4$  nAChR was 1.4 nM, with a B(max) of 10.3 pmol/mg protein, similar to what was determined for unlabeled AT-1012 using [(3)H]epibatidine. Saturation isotherms suggested that [<sup>125</sup>I]AT-1012 binds to a single site on the  $\alpha 3\beta 4$  nAChR. Similar high binding affinity was also observed for [<sup>125</sup>I]AT-1012 at the human  $\alpha 3\beta 4\alpha 5$  nAChR transfected into HEK cells. [<sup>125</sup>I]AT-1012 did not bind with high affinity to membranes from  $\alpha 4\beta 2$  nAChR-transfected HEK cells. Binding studies with [(3)H]epibatidine further confirmed that AT-1012 had over 100-fold binding selectivity for  $\alpha 3\beta 4$  over  $\alpha 4\beta 2$  nAChR. K(i) values determined for known nAChR compounds using [<sup>125</sup>I]AT-1012 as radioligand were comparable to those obtained with [(3)H]epibatidine. [<sup>125</sup>I]AT-1012 was also used to label  $\alpha 3\beta 4$  nAChR in rat brain slices in vitro using autoradiography, which showed highly localized binding of the radioligand in brain regions consistent with the discreet localization of the  $\alpha 3\beta 4$  nAChR. The authors demonstrate that [<sup>125</sup>I]AT-1012 is an excellent tool for labeling the  $\alpha 3\beta 4$  nAChR in the presence of other nAChR subtypes.

**Length Of Smoking Deprivation Moderates the Effects Of Alcohol Administration On Urge To Smoke** Day AM, Kahler CW, Spillane NS, Metrik J, Rohsenow DJ. Addict Behav. 2014 Feb; [Epub ahead of print].

Although smoking deprivation is often used in laboratory studies to induce urges to smoke cigarettes, the optimal length of deprivation has not been established. Previous research showed that overnight abstinence from cigarettes led to high baseline urge to smoke that potentially masked alcohol's acute effects on urge to smoke (Kahler et al., 2012). The current study examined whether alcohol's effects on smoking urge were more pronounced when a shorter length of smoking deprivation was used (i.e., 3h instead of overnight abstinence). Using a balanced placebo design for alcohol administration, the authors found that participants experienced a significant increase in self-reported urge to smoke when administered alcohol after a 3-h smoking deprivation (n=32), whereas this effect was smaller and nonsignificant when smokers were required to be abstinent overnight (n=96). Research on factors that heighten smoking urges may find stronger effects if a 3-h deprivation is used compared to using overnight abstinence.

**Therapeutic Infusions Of Ketamine: Do The Psychoactive Effects Matter?** Dakwar E, Anerella C, Hart CL, Levin FR, Mathew SJ, Nunes EV. Drug Alcohol Depend. 2014 Mar; 136 [Epub ahead of print] 153-157.

Sub-anesthetic ketamine infusions may benefit a variety of psychiatric disorders, including addiction. Though ketamine engenders transient alterations in consciousness, it is not known whether these alterations influence efficacy. This analysis evaluates the mystical-type effects of ketamine, which may have therapeutic potential according to prior research, and assesses whether these effects mediate improvements in dependence-related deficits, 24h postinfusion. Eight cocaine dependent individuals completed this double-blind, randomized, inpatient study. Three counter-balanced infusions separated by 48h were received: lorazepam (2mg) and two doses of ketamine (0.41mg/kg and 0.71mg/kg, with the former dose always preceding the latter). Infusions were followed within 15min by measures of dissociation (Clinician Administered Dissociative Symptoms Scale: CADSS) and mystical-type effects (adapted from Hood's Mysticism Scale: HMS). At baseline and 24h postinfusion, participants underwent assessments of motivation to stop cocaine (University of Rhode Island Change Assessment) and cue-induced craving (by visual analogue scale for cocaine craving during cue exposure). Ketamine led to significantly greater acute mystical-type effects (by HMS) relative to the active control lorazepam; ketamine 0.71mg/kg was associated with significantly higher HMS scores than was the 0.41mg/kg dose. HMS score, but not CADSS score, was found to mediate the effect of ketamine on motivation to quit cocaine 24h postinfusion. These findings suggest that psychological mechanisms may be involved in some of the anti-addiction benefits resulting from ketamine. Future research can evaluate whether the psychoactive effects of ketamine influence improvements in larger samples.

**A Two-Phased Screening Paradigm For Evaluating Candidate Medications For Cocaine Cessation Or Relapse Prevention: Modafinil, Levodopa-Carbidopa, Naltrexone** Schmitz JM, Green CE, Stotts AL, Lindsay JA, Rathnayaka NS, Grabowski J, Moeller FG. Drug Alcohol Depend. 2014 Mar; 136 [Epub ahead of print] 100-107.

Cocaine pharmacotherapy trials are often confounded by considerable variability in baseline cocaine-use levels, obscuring possible medication efficacy. Testing the feasibility of using a prerandomization, abstinence-induction protocol, the authors screened three candidate medications to explore treatment response in patients who did, or did not, achieve abstinence during an extended baseline phase. Eligible treatment-seeking, cocaine-dependent subjects entered a 4-week baseline period (Phase I) with high-value abstinence contingent vouchers and two motivational interviewing sessions, followed by a 12-week medication trial (Phase II) with random assignment stratified on Phase I abstinence status to

(1) modafinil (400mg/d), (2) levodopa/carbidopa (800/200mg/d), (3) naltrexone (50mg/d), or (4) placebo. Treatment consisted of thrice-weekly clinic visits for urine benzoylecgonine testing and weekly cognitive behavioral therapy with contingency management targeting medication compliance. Of the 118 subjects enrolled, 81 (80%) completed Phase I, with 33 (41%) achieving abstinence, defined a priori as 6 consecutive cocaine-negative urines. Tests of the interaction of each medication (active versus placebo) by baseline status (abstinent versus nonabstinent) permitted moderator effect analysis. Overall, baseline abstinence predicted better outcome. Cocaine-use outcomes for levodopa and naltrexone treatment differed as a function of Phase I abstinence status, with both medications producing benefit in nonabstinent but not baseline-abstinent subjects. There was no evidence of a moderator effect for modafinil. The two-phase screening trial demonstrated that subgrouping of patients with respect to baseline abstinence status is feasible and clinically useful for exploring cocaine cessation and relapse-prevention effects of candidate medications.

**Sex Differences In Guanfacine Effects On Drug Craving and Stress Arousal In Cocaine-Dependent Individuals**

Fox HC, Morgan PT, Sinha R. Neuropsychopharmacology. 2014 Jan; [Epub ahead of print].

Currently, no FDA-approved medication exists for the treatment of cocaine use disorder. Furthermore, as women become increasingly more at risk for the consequences of cocaine addiction, the need to establish better-tailored treatment medications is paramount. The authors examine the effects of the alpha2 adrenergic agonist, guanfacine HCl, on responses to stress and drug cue in a group of cocaine-dependent men and women who also abuse alcohol and nicotine. Forty early abstinent treatment-seeking cocaine-dependent males and females were randomly assigned to receive either daily placebo (12 M/7 F) or guanfacine (2 or 3mg) (15 M/6 F) for 3 weeks. In week 4, they participated in a laboratory experiment and were exposed to three 10-min guided imagery conditions (stress/stress, cue/cue, and stress/cue), one per day, consecutively in a random, counterbalanced order. Craving, negative emotion, anxiety, and cardiovascular function were assessed at baseline, immediately following imagery exposure, and at various recovery time points. Guanfacine significantly attenuated cocaine craving, alcohol craving, anxiety, and negative emotion following exposure to all three imagery conditions in females, but not males. Guanfacine did, however, reduce sympathetic tone as well as stress and cue-induced nicotine craving and systolic blood pressure (SBP) in both males and females. These findings highlight sex-specific effects of guanfacine on drug craving, anxiety, and negative mood with significant effects in women and not men. The findings suggest further evaluation of guanfacine in the treatment of cocaine use disorder with a specific focus on sex differences in treatment response. Neuropsychopharmacology advance online publication, 5 February 2014; doi:10.1038/npp. 2014. 1.

**Dysregulation Of Diurnal Cortisol Secretion Affects Abstinence Induction During A Lead-In Period Of A Clinical Trial For Depressed Cocaine-Dependent Patients**

Raby WN, Sanfilippo L, Pavlicova M, Carpenter KM, Glass A, Onyemekwu C, Roginek E, Nunes EV. Am J Addict. 2014; 23(1): 1-6.

Hypothesizing that stress dysregulation may worsen cocaine dependence, the authors investigated the effect of diurnal cortisol secretion profile, suppression of cortisol secretion, and total cortisol secretion on retention, abstinence-based voucher earnings, days of cravings, and mood status of participants at the end of a 2-week medication-free lead-in prior to randomization in a clinical trial of mirtazapine (60mg vs. placebo) for depressed cocaine-dependent patients. They measured saliva cortisol levels at 9AM, 2PM, and 5PM on the first two consecutive days of a 2-week medication-free lead-in period. Results from saliva samples were used to estimate the total daily level of cortisol, the diurnal profile of secretion (typical vs. atypical), and response to dexamethasone suppression (.1mg). Seventy-seven

patients collected saliva samples at baseline, and 65 (85%) were suitable for profile analysis. Patients with typical profiles (52%) collected significantly more abstinence-based voucher earnings during the lead-in ( $U=299.50$ ,  $p=.025$ ). Diurnal secretion profile did not significantly affect mood status, days of craving, or retention. There were no significant effects of suppression of cortisol secretion or of total cortisol levels on any outcome measures. In a subgroup of cocaine-dependent patients, deviation of cortisol secretion away from the homeostatic diurnal pattern was associated with reduced success at achieving early abstinence, an important determinant of treatment success.

#### **Differential Effects Of Non-Nicotine Tobacco Constituent Compounds On Nicotine Self-Administration In Rats**

Hall BJ, Wells C, Allenby C, Lin MY, Hao I, Marshall L, Rose JE, Levin ED. *Pharmacol Biochem Behav.* 2014 Feb; 120C [Epub ahead of print] 103-108.

Tobacco smoking has been shown to be quite addictive in people. However, nicotine itself is a weak reinforcer compared to other commonly abused drugs, leading speculation that other factors contribute to the high prevalence of tobacco addiction in the human population. In addition to nicotine, there are over 5000 chemical compounds that have been identified in tobacco smoke, and more work is needed to ascertain their potential contributions to tobacco's highly addictive properties, or as potential candidates for smoking cessation treatment. In this study, the authors examined seven non-nicotine tobacco constituent compounds (anabasine, anatabine, nornicotine, myosmine, harmane, norharmane, and tyramine) for their effects on nicotine self-administration behavior in rats. Young adult female Sprague-Dawley rats were allowed to self-administer nicotine (0.03mg/kg/50 $\mu$ l infusion) under a fixed ratio-1 schedule of reinforcement. Each self-administration session lasted 45 min. Doses of each tobacco constituent compound were administered subcutaneously 10 min prior to the start of each session in a repeated measures, counterbalanced order two times. Anabasine displayed a biphasic dose-effect function. Pretreatment with 0.02mg/kg anabasine resulted in a 25% increase in nicotine self-administration, while 2.0mg/kg of anabasine reduced nicotine infusions per session by over 50%. Pretreatment with 2.0mg/kg anatabine also significantly reduced nicotine self-administration by nearly half. These results suggest that some non-nicotine tobacco constituents may enhance or reduce nicotine's reinforcing properties. Also, depending upon the appropriate dose, some of these compounds may also serve as potential smoking cessation agents.

#### **Length Of Smoking Deprivation Moderates the Effects Of Alcohol Administration On Urge To Smoke**

Day AM, Kahler CW, Spillane NS, Metrik J, Rohsenow DJ. *Addict Behav.* 2014 Feb; [Epub ahead of print].

Although smoking deprivation is often used in laboratory studies to induce urges to smoke cigarettes, the optimal length of deprivation has not been established. Previous research showed that overnight abstinence from cigarettes led to high baseline urge to smoke that potentially masked alcohol's acute effects on urge to smoke (Kahler et al., 2012). The current study examined whether alcohol's effects on smoking urge were more pronounced when a shorter length of smoking deprivation was used (i.e., 3h instead of overnight abstinence). Using a balanced placebo design for alcohol administration, the authors found that participants experienced a significant increase in self-reported urge to smoke when administered alcohol after a 3-h smoking deprivation ( $n=32$ ), whereas this effect was smaller and nonsignificant when smokers were required to be abstinent overnight ( $n=96$ ). Research on factors that heighten smoking urges may find stronger effects if a 3-h deprivation is used compared to using overnight abstinence.

**A Double-Blind Placebo-Controlled Randomized Trial Of Varenicline For Smokeless Tobacco Dependence In India** Jain R, Jhanjee S, Jain V, Gupta T, Mittal S, Goelz P, Wileyto EP, Schnoll RA. *Nicotine Tob Res.* 2014 Jan; 16(1): 50-57.

The rate of smokeless tobacco use in India is 20%; its use causes serious health problems, and no trial has assessed behavioral or pharmacological treatments for this public health concern. This trial evaluated varenicline for treating smokeless tobacco dependence in India. This was a double-blind placebo-controlled randomized trial of varenicline (12 weeks, 1mg, twice per day) with 237 smokeless tobacco users in India. All participants received behavioral counseling. Outcomes included self-reported and biochemically verified abstinence at the end of treatment (EOT), lapse and recovery events, safety, and medication adherence. Self-reported EOT abstinence was significantly greater for varenicline (43%) versus placebo (31%; adjusted odds ratio [AOR] = 2.6, 95% CI = 1.2-4.2,  $p = .009$ ). Biochemically confirmed EOT abstinence was greater for varenicline versus placebo (25.2% vs. 19.5%), but this was not statistically different (AOR = 1.6, 95% CI = 0.84-3.1,  $p = .15$ ). Compared with placebo, varenicline did not reduce the risk for a lapse (hazard ratio [HR] = 0.86, 95% CI = 0.69-1.1,  $p = .14$ ), but it did increase the likelihood of recovery to abstinence (HR = 1.2, 95% CI = 1.02-1.4,  $p = .02$ ). Greater adherence increased EOT cessation rates for varenicline (39% vs. 18%,  $p = .003$ ) but not for placebo (28% vs. 14%,  $p = .06$ ). There were no significant differences between varenicline and placebo in rate of side effects, serious adverse events, hypertension, or stopping or reducing medication. Varenicline is safe for treating smokeless tobacco dependence in India, and further examination of this medication for this important public health problem is warranted.

**Maintenance Treatment With Varenicline For Smoking Cessation In Patients With Schizophrenia and Bipolar Disorder: A Randomized Clinical Trial** Evins AE, Cather C, Pratt SA, Pachas GN, Hoepfner SS, Goff DC, Achtyes ED, Ayer D, Schoenfeld DA. *JAMA.* 2014 Jan; 311(2): 145-154.

It is estimated that more than half of those with serious mental illness smoke tobacco regularly. Standard courses of pharmacotherapeutic cessation aids improve short-term abstinence, but most who attain abstinence relapse rapidly after discontinuation of pharmacotherapy. The goal of this study was to determine whether smokers diagnosed with schizophrenia and bipolar disease have higher rates of prolonged tobacco abstinence with maintenance pharmacotherapy than with standard treatment. Randomized, double-blind, placebo-controlled, parallel-group, relapse-prevention clinical trial conducted in 10 community mental-health centers. Of 247 smokers with schizophrenia or bipolar disease recruited from March 2008-April 2012, 203 received 12-weeks' open-label varenicline and cognitive behavioral therapy and 87 met abstinence criteria to enter the relapse prevention intervention. Participants who had 2 weeks or more of continuous abstinence at week 12 of open treatment were randomly assigned to receive cognitive behavioral therapy and double-blind varenicline (1 mg, 2 per day) or placebo from weeks 12 to 52. Participants then discontinued study treatment and were followed up to week 76. Seven-day rate of continuous abstinence at study week 52, the end of the relapse-prevention phase, confirmed by exhaled carbon monoxide. Secondary outcomes were continuous abstinence rates for weeks 12 through 64 based on biochemically verified abstinence and weeks 12 through 76, based on self-reported smoking behavior. Sixty-one participants completed the relapse-prevention phase; 26 discontinued participation (7 varenicline, 19 placebo) and were considered to have relapsed for the analyses; 18 of these had relapsed prior to dropout. At week 52, point-prevalence abstinence rates were 60% in the varenicline group (24 of 40) vs 19% (9 of 47) in the placebo group (odds ratio [OR], 6.2; 95% CI, 2.2-19.2;  $P < .001$ ). From weeks 12 through 64, 45% (18 of 40) among those in the varenicline group vs 15% (7 of 47) in the placebo group were continuously abstinent (OR, 4.6; 95% CI, 1.5-15.7;  $P = .004$ ), and from weeks 12 through 76, 30% (12 of 40) in the varenicline group vs 11% (5 of 47) in the placebo group were continuously abstinent (OR, 3.4; 95%

CI, 1.02-13.6;  $P=0.03$ ). There were no significant treatment effects on psychiatric symptom ratings or psychiatric adverse events. Among smokers with serious mental illness who attained initial abstinence with standard treatment, maintenance pharmacotherapy with varenicline and cognitive behavioral therapy improved prolonged tobacco abstinence rates compared with cognitive behavioral therapy alone after 1 year of treatment and at 6 months after treatment discontinuation. [clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00621777.

**A Double Blind, Within Subject Comparison Of Spontaneous Opioid Withdrawal From Buprenorphine Versus Morphine** Tompkins DA, Smith MT, Mintzer MZ, Campbell CM, Strain EC. J Pharmacol Exp Ther. 2014 Feb; 348(2): 217-226.

Preliminary evidence suggests that there is minimal withdrawal after the cessation of chronically administered buprenorphine and that opioid withdrawal symptoms are delayed compared with those of other opioids. The present study compared the time course and magnitude of buprenorphine withdrawal with a prototypical  $\mu$ -opioid agonist, morphine. Healthy, out-of-treatment opioid-dependent residential volunteers ( $N = 7$ ) were stabilized on either buprenorphine (32 mg/day i.m.) or morphine (120 mg/day i.m.) administered in four divided doses for 9 days. They then underwent an 18-day period of spontaneous withdrawal, during which four double-blind i.m. placebo injections were administered daily. Stabilization and spontaneous withdrawal were assessed for the second opioid using the same time course. Opioid withdrawal measures were collected eight times daily. Morphine withdrawal symptoms were significantly ( $P < 0.05$ ) greater than those of buprenorphine withdrawal as measured by mean peak ratings of Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), all subscales of the Profile of Mood States (POMS), sick and pain (0-100) Visual Analog Scales, systolic and diastolic blood pressure, heart rate, respiratory rate, and pupil dilation. Peak ratings on COWS and SOWS occurred on day 2 of morphine withdrawal and were significantly greater than on day 2 of buprenorphine withdrawal. Subjective reports of morphine withdrawal resolved on average by day 7. There was minimal evidence of buprenorphine withdrawal on any measure. In conclusion, spontaneous withdrawal from high-dose buprenorphine appears subjectively and objectively milder compared with that of morphine for at least 18 days after drug cessation.

**Extended Release Naltrexone Injection Is Performed In the Majority Of Opioid Dependent Patients Receiving Outpatient Induction: A Very Low Dose Naltrexone And Buprenorphine Open Label Trial** Mannelli P, Wu LT, Peindl KS, Swartz MS, Woody GE. Drug Alcohol Depend. 2014 Feb; [Epub ahead of print].

The approval of extended release injectable naltrexone (XR-NTX; Vivitrol®) has introduced a new option for treating opioid addiction, but studies are needed to identify its place within the spectrum of available therapies. The absence of physiological opioid dependence is a necessary and challenging first step for starting XR-NTX. Outpatient detoxification gives poor results and inpatient detoxification is either unavailable or too brief for the physiological effects of opioids to resolve. Here the authors present findings from an open label study that tested whether the transition from opioid addiction to XR-NTX can be safely and effectively performed in an outpatient setting using very low dose naltrexone and buprenorphine. Twenty treatment seeking opioid addicted individuals were given increasing doses of naltrexone starting at 0.25mg with decreasing doses of buprenorphine starting at 4mg during a 7-day outpatient XR-NTX induction procedure. Withdrawal discomfort, craving, drug use, and adverse events were assessed daily until the XR-NTX injection, then weekly over the next month. Fourteen of the 20 participants received XR-NTX and 13 completed weekly assessments. Withdrawal, craving, and opioid or other drug use were significantly lower during induction and after XR-NTX administration compared with baseline, and no serious adverse events were recorded.

Outpatient transition to XR-NTX combining upward titration of very low dose naltrexone with downward titration of low dose buprenorphine was safe, well tolerated, and completed by most participants. Further studies with larger numbers of subjects are needed to see if this approach is useful for naltrexone induction.

**Methadone and Buprenorphine-Naloxone Are Effective In Reducing Illicit Buprenorphine and Other Opioid Use, and Reducing HIV Risk Behavior--Outcomes Of A Randomized Trial**

Otiashvili D, Piralishvili G, Sikharulidze Z, Kamkamidze G, Poole S, Woody GE. Drug Alcohol Depend. 2013 Dec; 133(2): 376-382.

The objective of this study was to determine the extent to which buprenorphine injectors continue treatment with buprenorphine-naloxone or methadone, and the impact of these treatments on substance use and HIV risk in the Republic of Georgia. This was a randomized controlled 12-week trial of daily-observed methadone or buprenorphine-naloxone followed by a dose taper, referral to ongoing treatment, and follow-up at week 20 at the Uranti Clinic in Tbilisi, Republic of Georgia. Eighty consenting treatment-seeking individuals (40/group) aged 25 and above who met ICD-10 criteria for opioid dependence with physiologic features and reported injecting buprenorphine 10 or more times in the past 30 days. Opioid use according to urine tests and self-reports, treatment retention, and HIV risk behavior as determined by the Risk Assessment Battery. Mean age of participants was 33. 7 (SD5. 7), 4 were female, mean history of opioid injection use was 5. 8 years (SD4. 6), none were HIV+ at intake or at the 12-week assessment and 73. 4% were HCV+. Sixty-eight participants (85%) completed the 12-week medication phase (33 from methadone and 35 from buprenorphine/naloxone group); 37 (46%) were in treatment at the 20-week follow-up (21 from methadone and 16 from the buprenorphine/naloxone group). In both study arms, treatment resulted in a marked reduction in unprescribed buprenorphine, other opioid use, and HIV injecting risk behavior with no clinically significant differences between the two treatment arms. Daily observed methadone or buprenorphine-naloxone are effective treatments for non-medical buprenorphine and other opioid use in the Republic of Georgia and likely to be useful for preventing HIV infection.

## **RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS**

**Changes in HIV Incidence among People Who Inject Drugs in Taiwan following Introduction of a Harm Reduction Program: A Study of Two Cohorts** Huang Y-F, Yang J-Y, Nelson KE, Kuo H-S, Lew-Ting C-Y, et al. PLoS Med 2014;11(4): e1001625. doi:10.1371/journal.pmed.1001625.

Harm reduction strategies for combating HIV epidemics among people who inject drugs (PWID) have been implemented in several countries. However, large-scale studies using sensitive measurements of HIV incidence and intervention exposures in defined cohorts are rare. The aim of this study was to determine the association between harm reduction programs and HIV incidence among PWID. The study included two populations. For 3,851 PWID who entered prison between 2004 and 2010 and tested HIV positive upon incarceration, The authors tested their sera using a BED HIV-1 capture enzyme immunoassay to estimate HIV incidence. Also, they enrolled in a prospective study a cohort of 4,357 individuals who were released from prison via an amnesty on July 16, 2007. The authors followed them with interviews at intervals of 6–12 mo and by linking several databases. A total of 2,473 participants who were HIV negative in January 2006 had interviews between then and 2010 to evaluate the association between use of harm reduction programs and HIV incidence. The authors used survival methods with attendance at methadone clinics as a time-varying covariate to measure the association with HIV incidence. They used a Poisson regression model and calculated the HIV incidence rate to evaluate the association between needle/syringe program use and HIV incidence. Among the population of PWID who were imprisoned, the implementation of comprehensive harm reduction programs and a lower mean community HIV viral load were associated with a reduced HIV incidence among PWID. The HIV incidence in this population of PWID decreased from 18.2% in 2005 to 0.3% in 2010. In an individual-level analysis of the amnesty cohort, attendance at methadone clinics was associated with a significantly lower HIV incidence (adjusted hazard ratio: 0.20, 95% CI: 0.06–0.67), and frequent users of needle/syringe program services had lower HIV incidence (0% in high NSP users, 0.5% in non NSP users). In addition, no HIV seroconversions were detected among prison inmates. The authors conclude that although their data are affected by participation bias, they strongly suggest that comprehensive harm reduction services and free treatment were associated with reversal of a rapidly emerging epidemic of HIV among PWID.

**Expansion of HAART Coverage Is Associated with Sustained Decreases in HIV/AIDS Morbidity, Mortality and HIV Transmission: The “HIV Treatment as Prevention” Experience in a Canadian Setting** Montaner JS, Lima VD, Harrigan PR, Lourenço L, Yip B, et al. PLoS ONE 2014; 9(2): e87872. doi:10.1371/journal.pone.0087872.

There has been renewed call for the global expansion of highly active antiretroviral therapy (HAART) under the framework of HIV treatment as prevention (TasP). However, population-level sustainability of this strategy has not been characterized. The authors used population-level longitudinal data from province-wide registries including plasma viral load, CD4 count, drug resistance, HAART use, HIV diagnoses, AIDS incidence, and HIV-related mortality. They fitted two Poisson regression models over the study period, to relate estimated HIV incidence and the number of individuals on HAART and the percentage of virologically suppressed individuals. HAART coverage, median pre-HAART CD4 count, and HAART adherence increased over time and were associated with increasing virological suppression and decreasing drug resistance. AIDS incidence decreased from 6.9 to 1.4 per 100,000 population (80% decrease,  $p = 0.0330$ ) and HIV-related mortality decreased from 6.5 to 1.3 per 100,000 population (80% decrease,  $p = 0.0115$ ). New HIV diagnoses declined from 702 to 238 cases (66% decrease;  $p = 0.0004$ ) with a consequent estimated decline in HIV incident cases from 632 to 368 cases per year (42% decrease;  $p = 0.0003$ ). Finally, the authors' models suggested that for each



increase of 100 individuals on HAART, the estimated HIV incidence decreased 1.2% and for every 1% increase in the number of individuals suppressed on HAART, the estimated HIV incidence also decreased by 1%. These results show that HAART expansion between 1996 and 2012 in BC was associated with a sustained and profound population-level decrease in morbidity, mortality and HIV transmission. These findings support the long-term effectiveness and sustainability of HIV treatment as prevention within an adequately resourced environment with no financial barriers to diagnosis, medical care or antiretroviral drugs. The 2013 Consolidated World Health Organization Antiretroviral Therapy Guidelines offer a unique opportunity to further evaluate TasP in other settings, particularly within generalized epidemics, and resource-limited setting, as advocated by UNAIDS.

### **Effects Of Early Versus Delayed Initiation Of Antiretroviral Treatment On Clinical Outcomes Of HIV-1 Infection: Results From the Phase 3 HPTN 052 Randomised Controlled Trial**

Grinsztejn B, Hosseinipour, MC, Ribaudo HJ, Swindells S et al. The Lancet Infectious Diseases.1 April 2014; 14(4): 281-290.DOI: 10.1016/S1473-3099(13)70692-3.

Use of antiretroviral treatment for HIV-1 infection has decreased AIDS-related morbidity and mortality and prevents sexual transmission of HIV-1. However, the best time to initiate antiretroviral treatment to reduce progression of HIV-1 infection or non-AIDS clinical events is unknown. The authors reported previously that early antiretroviral treatment reduced HIV-1 transmission by 96%. They aimed to compare the effects of early and delayed initiation of antiretroviral treatment on clinical outcomes. The HPTN 052 trial is a randomised controlled trial done at 13 sites in nine countries. The authors enrolled HIV-1-serodiscordant couples to the study and randomly allocated them to either early or delayed antiretroviral treatment by use of permuted block randomisation, stratified by site. Random assignment was unblinded. The HIV-1-infected member of every couple initiated antiretroviral treatment either on entry into the study (early treatment group) or after a decline in CD4 count or with onset of an AIDS-related illness (delayed treatment group). Primary events were AIDS clinical events (WHO stage 4 HIV-1 disease, tuberculosis, and severe bacterial infections) and the following serious medical conditions unrelated to AIDS: serious cardiovascular or vascular disease, serious liver disease, end-stage renal disease, new-onset diabetes mellitus, and non-AIDS malignant disease. Analysis was by intention-to-treat. This trial is registered with [ClinicalTrials.gov](http://ClinicalTrials.gov), number [NCT00074581](https://clinicaltrials.gov/ct2/show/study/NCT00074581). 1763 people with HIV-1 infection and a serodiscordant partner were enrolled in the study; 886 were assigned early antiretroviral treatment and 877 to the delayed treatment group (two individuals were excluded from this group after randomisation). Median CD4 counts at randomisation were 442 (IQR 373—522) cells per  $\mu\text{L}$  in patients assigned to the early treatment group and 428 (357—522) cells per  $\mu\text{L}$  in those allocated delayed antiretroviral treatment. In the delayed group, antiretroviral treatment was initiated at a median CD4 count of 230 (IQR 197—249) cells per  $\mu\text{L}$ . Primary clinical events were reported in 57 individuals assigned to early treatment initiation versus 77 people allocated to delayed antiretroviral treatment (hazard ratio 0.73, 95% CI 0.52—1.03;  $p=0.074$ ). New-onset AIDS events were recorded in 40 participants assigned to early antiretroviral treatment versus 61 allocated delayed initiation (0.64, 0.43—0.96;  $p=0.031$ ), tuberculosis developed in 17 versus 34 patients, respectively (0.49, 0.28—0.89,  $p=0.018$ ), and primary non-AIDS events were rare (12 in the early group vs nine with delayed treatment). In total, 498 primary and secondary outcomes occurred in the early treatment group (incidence 24.9 per 100 person-years, 95% CI 22.5—27.5) versus 585 in the delayed treatment group (29.2 per 100 person-years, 26.5—32.1;  $p=0.025$ ). 26 people died, 11 who were allocated to early antiretroviral treatment and 15 who were assigned to the delayed treatment group. Early initiation of antiretroviral treatment delayed the time to AIDS events and decreased the incidence of primary and secondary outcomes. The clinical benefits recorded, combined with the striking reduction in HIV-1 transmission risk previously reported, provides strong support for earlier initiation of antiretroviral treatment. Funding: NIAID.

### **Do Metropolitan HIV Epidemic Histories and Programs For People Who Inject Drugs and Men Who Have Sex With Men Predict AIDS Incidence and Mortality Among Heterosexuals?**

Friedman SR, West BS, Tempalski B, Morton CM, Cleland CM, Des Jarlais DC, Hall HI, Cooper HLF. *Annals of Epidemiology* 2014; 24(4): 304–311.

The authors focus on a little-researched issue—how human immunodeficiency virus (HIV) epidemics and programs in key populations in metropolitan areas affect epidemics in other key populations. They consider (1) How are earlier epidemics among people who inject drugs (PWID) and men who have sex with men (MSM) related to later AIDS incidence and mortality among heterosexuals?; (2) Were prevention programs targeting PWID or MSM associated with lower AIDS incidence and mortality among heterosexuals?; and (3) Was the size of the potential bridge population of noninjecting drug users (NIDUs) in a metropolitan area associated with later AIDS incidence and mortality among heterosexuals? Using data for 96 large U.S. metropolitan areas, Poisson regression assessed associations of population prevalences of HIV-infected PWID and MSM (1992); NIDU population prevalence (1992–1994); drug use treatment coverage for PWID (1993); HIV counseling and testing coverage for MSM and for PWID (1992); and syringe exchange presence (2000) with CDC data on AIDS incidence and mortality among heterosexuals in 2006–2008, with appropriate socioeconomic controls. Population density of HIV+ PWID and of NIDUs were positively related, and prevention programs for PWID negatively related to later AIDS incidence among heterosexuals and later mortality among heterosexuals living with AIDS. HIV+ MSM population density and prevention programs for MSM were not associated with these outcomes. The authors conclude that efforts to reduce HIV transmission among PWID and NIDUs may reduce AIDS and AIDS-related mortality among heterosexuals. More research is needed at metropolitan area, network, and individual levels into HIV bridging across key populations and how interventions in one key population affect HIV epidemics in other key populations.

### **Prevention and Treatment Produced Large Decreases In HIV Incidence In A Model Of People Who Inject Drugs**

Marshall BD, Friedman SR, Monteiro JF, Paczkowski M, Tempalski B, Pouget ER, Lurie MN, Galea S. *Health Aff (Millwood)*. 2014 Mar; 33(3): 401-409. doi: 10.1377/hlthaff.2013.0824.

In the United States, people who inject drugs continue to be at greatly increased risk of HIV infection. To estimate the effectiveness of various prevention scenarios, the authors modeled HIV transmission in a dynamic network of drug users and people who did not use drugs that was based on the New York Metropolitan Statistical Area population. They compared the projected HIV incidence in 2020 and 2040 if current approaches continue to be used to the incidence if one or more of the following hypothetical interventions were applied: increased HIV testing, improved access to substance abuse treatment, increased use of needle and syringe programs, scaled-up treatment as prevention, and a "high impact" combination scenario, consisting of all of the strategies listed above. No strategy completely eliminated HIV transmission. The high-impact combination strategy produced the largest decrease in HIV incidence—a 62 percent reduction compared to the status quo. These results suggest that increased resources for and investments in multiple HIV prevention approaches will be required to eliminate HIV transmission among people who inject drugs.

### **Impact Of Protective Killer Inhibitory Receptor/Human Leukocyte Antigen Genotypes On Natural Killer Cell and T-Cell Function In HIV-1-Infected Controllers**

Tomescu C, Duh FM, Hoh R, Viviani A, Harvill K, Martin MP, Carrington M, Deeks SG, Montaner LJ. *AIDS*. 2012 Sep; 26(15): 1869-1878.

Both protective T-cell genotypes and natural killer (NK) cell genotypes have been associated with delayed progression to AIDS and shown to be co-inherited in HIV-1-infected individuals who limit

viral replication in absence of antiretroviral therapy ('controllers'). However, a comparative analysis of the genotype and function of the innate and adaptive immune compartments in HIV-1-infected controller individuals has been understudied to date. Here, the authors simultaneously tested NK and T-cell function in controllers to investigate the mechanism(s) that might account for host immune control over viral replication. They measured CD8 T-cell responses against HIV-1 utilizing overlapping 15-mer peptides spanning the HIV-1 consensus clade B Gag protein and tested NK cell degranulation and cytokine secretion against tumor target cells following interferon- $\alpha$  (IFN $\alpha$ ) stimulation. Among a cohort of 37 controllers, the presence of protective major histocompatibility complex class I human leukocyte antigen (HLA) alleles (such as HLA-B\*57) was not correlated with HIV-specific CD8 responses. In contrast, the inheritance of a protective killer inhibitory receptor KIR3DL1\*h/\*y receptor genotype along with the corresponding HLA-Bw4\*80I ligand was associated with significantly heightened target cell-induced NK degranulation and cytokine secretion following IFN $\alpha$  stimulation ( $P = 0.0201$ ,  $n = 13$ ). Interestingly, the authors observed a significant inverse association between the IFN $\alpha$  stimulated NK response to K562 cells and the HIV-specific CD8 T-cell response to Gag among elite controllers ( $\rho = -0.8321$ ,  $P = 0.0010$ ,  $n = 12$ ). Together, these results suggest that heightened NK responses can be evidenced independently of HIV-specific T-cell responses in HIV-1-infected elite controllers.

**Correlates Of Non-Adherence To Antiretroviral Therapy In A Cohort Of HIV-Positive Drug Users Receiving Antiretroviral Therapy In Hanoi, Vietnam**

Jordan M, Obeng-Aduasare Y, Sheehan H, Hong S, Terrin N, Duong D, Trung N, Wanke C, Kinh N, Tang A. Int J STD AIDS. 2013 Dec; [Epub ahead of print].

The HIV epidemic in Vietnam is concentrated, with high prevalence estimates among injection drug users and commercial sex workers. Socio-demographics, substance use and clinical correlates of antiretroviral therapy non-adherence were studied in 100 HIV-1 infected drug users receiving antiretroviral therapy for at least 6 months in Hanoi, Vietnam. All study participants were men with a mean age of  $29.9 \pm 4.9$  years. The median duration on antiretroviral therapy was  $16.2 \pm 12.7$  months; 83% reported 'very good' or 'perfect' adherence in the past 30 days on a subjective one-item Likert scale at time of study enrollment; 48% of participants reported drug use within the previous 6 months, with 22% reporting current drug use. Injection drug use with or without non-injection drug use in the past 6 months (95% C.I. 2.19, 1.30-3.69) and years on antiretroviral therapy (95% C.I. 1.43, 1.14-1.78) were correlated with suboptimal adherence. These findings support Vietnam's ongoing scale-up of harm reduction programs for injection drug users and their integration with antiretroviral therapy delivery. Moreover, results highlight the need to identify and implement new ways to support high levels of antiretroviral therapy adherence as duration on antiretroviral therapy increases.

**Contemplating Abortion: HIV-Positive Women's Decision To Terminate Pregnancy**

Maccarthy S, Rasanathan JJ, Crawford-Roberts A, Dourado I, Gruskin S. Cult Health Sex. 2014; 16(2): 190-201. Research on pregnancy termination largely assumes HIV status is the only reason why HIV-positive women contemplate abortion. As antiretroviral treatment (ART) becomes increasingly available and women are living longer, healthier lives, the time has come to consider the influence of other factors on HIV-positive women's reproductive decision-making. Because ART has been free and universally available to Brazilians for more than two decades, Brazil provides a unique context in which to explore these issues. A total of 25 semi-structured interviews exploring women's pregnancy termination decision-making were conducted with women receiving care at the Reference Centre for HIV/AIDS in Salvador, Brazil. Interviews were transcribed, translated into English and coded for analysis. HIV played different roles in women's decision-making. In all, 13 HIV-positive women did not consider terminating their pregnancy. Influential factors described by those who did consider terminating their

pregnancy included fear of HIV transmission, fear of HIV-related stigma, family size, economic constraints, partner and provider influence, as well as lack of access to pregnancy termination services and abortifacients. For some HIV-positive women in Brazil, HIV can be the only reason to consider terminating a pregnancy, but other factors are significant. A thorough understanding of all variables affecting reproductive decision-making is necessary for enhancing services and policies and better meeting the needs and rights of HIV-positive women.

#### **Effects Of Alpha Interferon Treatment On Intrinsic Anti-HIV-1 Immunity In Vivo**

Abdel-Mohsen M, Deng X, Liegler T, Guatelli JC, Salama MS, Ghanem Hel-D, Rauch A, Ledergerber B, Deeks SG, Günthard HF, Wong JK, Pillai SK. J Virol. 2014 Jan; 88(1): 763-767.

Alpha interferon (IFN- $\alpha$ ) suppresses human immunodeficiency virus type 1 (HIV-1) replication in vitro by inducing cell-intrinsic retroviral restriction mechanisms. The authors investigated the effects of IFN- $\alpha$ /ribavirin (IFN- $\alpha$ /riba) treatment on 34 anti-HIV-1 restriction factors in vivo. Expression of several anti-HIV-1 restriction factors was significantly induced by IFN- $\alpha$ /riba in HIV/hepatitis C virus (HCV)-coinfected individuals. Fold induction of cumulative restriction factor expression in CD4(+) T cells was significantly correlated with viral load reduction during IFN- $\alpha$ /riba treatment ( $r(2) = 0.649$ ;  $P < 0.016$ ). Exogenous IFN- $\alpha$  induces supraphysiologic restriction factor expression associated with a pronounced decrease in HIV-1 viremia.

#### **Cocaine Enhances HIV-1 Infectivity In Monocyte Derived Dendritic Cells By Suppressing**

**MicroRNA-155** Napuri J, Pilakka-Kanthikeel S, Raymond A, Agudelo M, Yndart-Arias A, Saxena SK, Nair M. PLoS One. 2013; 8(12): e83682.

Cocaine and other drugs of abuse increase HIV-induced immunopathogenesis; and neurobiological mechanisms of cocaine addiction implicate a key role for microRNAs (miRNAs), single-stranded non-coding RNAs that regulate gene expression and defend against viruses. In fact, HIV defends against miRNAs by actively suppressing the expression of polycistronic miRNA cluster miRNA-17/92, which encodes miRNAs including miR-20a. IFN- $\gamma$  production by natural killer cells is regulated by miR-155 and this miRNA is also critical to dendritic cell (DC) maturation. However, the impact of cocaine on miR-155 expression and subsequent HIV replication is unknown. The authors examined the impact of cocaine on two miRNAs, miR-20a and miR-155, which are integral to HIV replication, and immune activation. Using miRNA isolation and analysis, RNA interference, quantitative real time PCR, and reporter assays they explored the effects of cocaine on miR-155 and miR-20 in the context of HIV infection. Here they demonstrate using monocyte-derived dendritic cells (MDCCs) that cocaine significantly inhibited miR-155 and miR-20a expression in a dose dependent manner. Cocaine and HIV synergized to lower miR-155 and miR-20a in MDCCs by 90%. Cocaine treatment elevated LTR-mediated transcription and PU. 1 levels in MDCCs. But in context of HIV infection, PU. 1 was reduced in MDCCs regardless of cocaine presence. Cocaine increased DC-SIGN and decreased CD83 expression in MDCC, respectively. Overall, the authors show that cocaine inhibited miR-155 and prevented maturation of MDCCs; potentially, resulting in increased susceptibility to HIV-1. These findings could lead to the development of novel miRNA-based therapeutic strategies targeting HIV infected cocaine abusers.

#### **HIV Viremia and T-Cell Activation Differentially Affect the Performance Of Glomerular Filtration Rate Equations Based On Creatinine and Cystatin C**

Bhasin B, Lau B, Atta MG, Fine DM, Estrella MM, Schwartz GJ, Lucas GM. PLoS One. 2013; 8(12): e82028.

Serum creatinine and cystatin C are used as markers of glomerular filtration rate (GFR). The performance of these GFR markers relative to exogenously measured GFR (mGFR) in HIV-positive individuals is not well established. The authors assessed the performance of the chronic kidney disease

epidemiology collaboration equations based on serum concentrations of creatinine (eGFR<sub>cr</sub>), cystatin C (eGFR<sub>cys</sub>) and both biomarkers combined (eGFR<sub>cr-cys</sub>) in 187 HIV-positive and 98 HIV-negative participants. Measured GFR was calculated by plasma iothexol clearance. Bias and accuracy were defined as the difference between eGFR and mGFR and the percentage of eGFR observations within 30% of mGFR, respectively. Activated CD4 and CD8 T-cells (CD38<sup>+</sup> HLA-DR<sup>+</sup>) were measured by flow cytometry. The median mGFR was >100 ml/min/1.73 m<sup>2</sup> in both groups. All equations tended to be less accurate in HIV-positive than in HIV-negative subjects, with eGFR<sub>cr-cys</sub> being the most accurate overall. In the HIV-positive group, eGFR<sub>cys</sub> was significantly less accurate and more biased than eGFR<sub>cr</sub> and eGFR<sub>cr-cys</sub>. Additionally eGFR<sub>cys</sub> bias and accuracy were strongly associated with use of antiretroviral therapy, HIV RNA suppression, and percentages of activated CD4 or CD8 T-cells. Hepatitis C seropositivity was associated with larger eGFR<sub>cys</sub> bias in both HIV-positive and HIV-negative groups. In contrast, eGFR<sub>cr</sub> accuracy and bias were not associated with HIV-related factors, T-cell activation, or hepatitis C. The performance of eGFR<sub>cys</sub> relative to mGFR was strongly correlated with HIV treatment factors and markers of T-cell activation, which may limit its usefulness as a GFR marker in this population.

**More Than Two Hands To Tango** Kolson D, Buch S. J Neuroimmune Pharmacol. 2013 Dec; 8(5): 1051-1054.

Developing a validated tool for the rapid and efficient assessment of cognitive functioning in HIV-infected patients in a typical outpatient clinical setting has been an unmet goal of HIV research since the recognition of the syndrome of HIV-associated dementia (HAD) nearly 20 years ago. In this issue of JNIP Cross et al. report the application of the International HIV Dementia Scale (IHDS) in a U. S. -based urban outpatient clinic to evaluate its utility as a substitute for the more time- and effort-demanding formalized testing criteria known as the Frascati criteria that was developed in 2007 to define the syndrome of HIV-associated neurocognitive disorders (HAND). In this study an unselected cohort of 507 individuals (68 % African American) that were assessed using the IHDS in a cross-sectional study revealed a 41 % prevalence of cognitive impairment (labeled ‘symptomatic HAND’) that was associated with African American race, older age, unemployment, education level, and depression. While the associations between cognitive impairment and older age, education, unemployment status and depression in HIV-infected patients are not surprising, the association with African American ancestry and cognitive impairment in the setting of HIV infection is a novel finding of this study. This commentary discusses several important issues raised by the study, including the pitfalls of assessing cognitive functioning with rapid screening tools, cognitive testing criteria, normative testing control groups, accounting for HAND co-morbidity factors, considerations for clinical trials assessing HAND, and selective population vulnerability to HAND.

**HIV-1/Cocaine Induced Oxidative Stress Disrupts Tight Junction Protein-1 In Human Pulmonary Microvascular Endothelial Cells: Role Of Ras/Erk1/2 Pathway** Dalvi P, Wang K, Mermis J, Zeng R, Sanderson M, Johnson S, Dai Y, Sharma G, Ladner AO, Dhillon NK. PLoS One. 2014; 9(1): e85246.

Intravenous drug use (IVDU) is the major risk factor in the development of HIV-related pulmonary arterial hypertension (HRPAH); however, the pathogenesis of HRPAH in association with IVDU has yet to be characterized. Endothelial injury is considered to be an initiating factor for pulmonary vascular remodeling in animal models of PAH. The authors’ previous study shows that simultaneous exposure to HIV-Trans-activator of transcription (Tat) and cocaine exacerbates both disruption of tight junction proteins and permeability of human pulmonary artery endothelial cells compared with either treatment alone. They here now demonstrate that this HIV-Tat and cocaine mediated endothelial dysfunction accompanies with increase in hydrogen peroxide and superoxide radicals generation and

involves redox sensitive signaling pathway. Pretreatment with antioxidant cocktail attenuated the cocaine and Tat mediated disassembly of Zonula Occludens (ZO)-1 and enhancement of endothelial monolayer permeability. Furthermore, inhibition of NADPH oxidase by apocynin or siRNA-mediated knockdown of gp-91(phox) abolished the Tat/cocaine-induced reactive oxygen species (ROS) production, suggesting the NADPH oxidase mediated generation of oxidative radicals. In addition, ROS dependent activation of Ras and ERK1/2 Kinase was observed to be mediating the TJP-1 disassembly, and endothelial dysfunction in response to cocaine and Tat exposure. In conclusion, these findings demonstrate that Tat/cocaine -mediated production of ROS activate Ras/Raf/ERK1/2 pathway that contributes to disruption of tight junction protein leading to pulmonary endothelial dysfunction associated with pulmonary vascular remodeling.

**Enhanced Nicotine Metabolism In HIV-1-Positive Smokers Compared With HIV-Negative Smokers: Simultaneous Determination Of Nicotine and Its Four Metabolites In Their Plasma Using A Simple and Sensitive Electrospray Ionization Liquid Chromatography-Tandem Mass Spectrometry Technique** Earla R, Ande A, McArthur C, Kumar A, Kumar S. Drug Metab Dispos. 2014 Feb; 42(2): 282-293.

Smoking is approximately three times more prevalent in HIV-1-positive than HIV-negative individuals in the United States. Nicotine, which is the major constituent of tobacco, is rapidly metabolized mainly by cytochrome P450 (CYP2A6) to many metabolites. In this study, the authors developed a simple, fast, and sensitive electrospray ionization liquid chromatography-tandem mass spectrometry method using a strong cation solid phase extraction, and determined the concentration of nicotine and its four major metabolites (cotinine, nornicotine, norcotinine, and trans-3'-hydroxycotinine) in the plasma of HIV-1-positive and HIV-negative smokers. The multiple reaction monitoring transitions for nicotine, cotinine, trans-3'-hydroxycotinine, nornicotine, norcotinine, nicotine-d<sub>4</sub>, and cotinine-d<sub>3</sub> were selected at mass-to-charge ratios of 163.3/117.1, 177.5/80.3, 193.2/80.1, 149.5/132.3, 163.4/80.3, 167.3/121.4, and 180.3/101.2, respectively. The lower limit of quantitation for nicotine and its metabolites was 0.53 ng/ml, which is relatively more sensitive than those previously reported. The concentration of nicotine was detected 5-fold lower in HIV-1-positive smokers ( $7.17 \pm 3.8$  ng/ml) than that observed in HIV-negative smokers ( $33.29 \pm 15.4$  ng/ml), whereas the concentration of the metabolite nornicotine was 3-fold higher in HIV-1-positive smokers ( $6.8 \pm 2.9$  ng/ml) than in HIV-negative smokers ( $2.3 \pm 1.2$  ng/ml). Although it was statistically nonsignificant, the concentration of the metabolite cotinine was also higher in HIV-1-positive smokers ( $85.6 \pm 60.5$  ng/ml) than in HIV-negative smokers ( $74.9 \pm 40.5$  ng/ml). In conclusion, a decrease in the concentration of nicotine and an increase in the concentration of its metabolites in HIV-1-positive smokers compared with HIV-negative smokers support the hypothesis that nicotine metabolism is enhanced in HIV-1-positive smokers compared with HIV-negative smokers.

**Vitamin D Status Of Human Immunodeficiency Virus-Positive Patients With Advanced Liver Disease Enrolled In the Solid Organ Transplantation In HIV: Multi-Site Study** Branch AD, Barin B, Rahman A, Stock P, Schiano TD. Liver Transpl. 2014 Feb; 20(2): 156-164.

An optimal vitamin D status may benefit liver transplantation (LT) patients. Higher levels of 25-hydroxyvitamin D [25(OH)D] mitigate steroid-induced bone loss after LT, correlate with better hepatitis C virus treatment responses, and increase graft survival. This study investigated 25(OH)D levels and assessed strategies for vitamin D deficiency prevention in human immunodeficiency virus (HIV)-positive patients with advanced liver disease who were enrolled in the Solid Organ Transplantation in HIV: Multi-Site Study. 25(OH)D was measured in banked specimens from 154 LT candidates/recipients with the DiaSorin assay; deficiency was defined as a 25(OH)D level <20 ng/mL. Information about vitamin D supplement use after LT was obtained from medication logs and via

surveys. Logistic regression, Cox regression, and linear repeated measures analyses were performed with SAS software. The authors found that none of the 17 academic medical centers in the United States routinely recommended vitamin D supplements before LT, and only a minority (4/17) recommended vitamin D supplements to all patients after LT. Seventy-one percent of the 139 patients with pre-LT values had vitamin D deficiency, which was significantly associated with cirrhosis ( $P=0.01$ ) but no other variable. The vitamin D status improved modestly after LT; however, the status was deficient for 40% of the patients 1 year after LT. In a multivariate linear repeated measures model, a higher pre-LT 25(OH)D level ( $P<0.001$ ), specimen collection in the summer ( $P<0.001$ ), a routine vitamin D supplementation strategy after LT ( $P<0.001$ ), and the time elapsing since LT ( $P=0.01$ ) were significantly associated with increases in the post-LT 25(OH)D level; black race was associated with a decreased level ( $P=0.02$ ). In conclusion, the majority of patients awaiting LT were vitamin D deficient, and approximately half were vitamin D deficient after LT. More extensive use of vitamin D supplements, more sun exposure, or both are needed to prevent this deficiency in HIV-positive LT candidates and recipients.

### **Hepatitis C Infection In Non-Treatment-Seeking Heroin Users: The Burden Of Cocaine Injection**

Roux P, Fugon L, Jones JD, Comer SD. Am J Addict. 2013; 22(6): 613-618.  
In heroin dependent individuals, the HIV epidemic has been controlled in countries where access to opioid maintenance treatment (OMT) and needle exchange programs (NEP) have been implemented. However, despite similar routes of contamination for both viruses, the prevalence of hepatitis C (HCV) infection remains high in drug users. The objective of this analysis was to identify the prevalence of HCV and the correlates of being HCV-positive in a sample of out-of-treatment heroin-dependent individuals. Data were collected from five inpatient studies ( $n = 120$  participants) conducted at the New York State Psychiatric Institute. A logistic regression was used to identify correlates of being HCV-positive at baseline. Among the 120 heroin-dependent volunteers, 42 were HCV-positive. Participants who had heavier alcohol use, a longer duration of heroin use, or who reported using heroin by injection were more likely to be HCV-positive. Interestingly, participants who had injected cocaine during the previous month had a nine-fold greater risk of being HCV-positive compared to non-cocaine users and those who used cocaine by a non-injecting route. These findings confirm the risk of being HCV-infected through intravenous drug use, especially with cocaine use. These results underscore the importance of rethinking interventions to prevent HCV infection with combined strategies using pharmacological approaches for cocaine dependence and tailored prevention for cocaine users.

### **Clearance Of Hepatitis C Infection Is Associated With Early Appearance Of Broad Neutralizing Antibody Responses**

Osburn WO, Snider AE, Wells BL, Latanich R, Bailey JR, Thomas DL, Cox AL, Ray SC. Hepatology. 2014 Jan; [Epub ahead of print].  
The contribution of humoral immune responses to spontaneous control of Hepatitis C virus (HCV) infection remains unclear. The authors assessed nAb responses during acute HCV infection to determine whether infection outcome is associated with the neutralizing antibody (nAb) response, specifically its timing or breadth (neutralization of multiple genotype-matched variants). A representative genotype 1 HCV pseudoparticle (HCVpp) library, consisting of 19 genetically-distinct genotype 1 HCVpp that comprise the natural variability of genotype 1 E1E2 sequences, was used to assess anti-genotype 1 nAb responses during acute infection in at-risk persons followed prospectively. Neutralization of individual library HCVpp by the last viremic plasma sample obtained before clearance was compared to either one-year post-initial viremia or clearance time-matched specimens obtained from subjects developing persistent infection. In persistently infected persons nAb responses were delayed then progressively broadened whereas in persons who controlled viremia broader

responses were detected early and contracted after clearance of viremia. Surprisingly, the breadth of anti-genotype 1 nAb responses was not dependent upon subjects' infection genotype. Also, individual library HCVpp neutralization sensitivity was not associated with any known E2 sequence determinants. Interestingly, two single nucleotide polymorphisms in the HLA-DQ locus were associated with nAb breadth. Taken together, these data demonstrate that control of HCV infection is associated with more rapid development of a broad nAb response, independent of the infection viral genotype, providing further evidence for the role of nAb in controlling HCV infection and the potential benefit of generating broad anti-HCV nAb responses by vaccination. (Hepatology 2014;).

**High Frequency Of False-Positive Hepatitis C Virus Enzyme-Linked Immunosorbent Assay In Rakai, Uganda** Mullis CE, Laeyendecker O, Reynolds SJ, Ocama P, Quinn J, Boaz I, Gray RH, Kirk GD, Thomas DL, Quinn TC, Stabinski L. Clin Infect Dis. 2013 Dec; 57(12): 1747-1750.

The prevalence of hepatitis C virus (HCV) infection in sub-Saharan Africa remains unclear. The authors tested 1000 individuals from Rakai, Uganda, with the Ortho version 3.0 HCV enzyme-linked immunosorbent assay. All serologically positive samples were tested for HCV RNA. Seventy-six of the 1000 (7.6%) participants were HCV antibody positive; none were confirmed by detection of HCV RNA.

**Cohort Profile: The International Collaboration Of Incident HIV and Hepatitis C In Injecting Cohorts (Inc3) Study** Grebely J, Morris MD, Rice TM, Bruneau J, Cox AL, Kim AY, McGovern BH, Shoukry NH, Lauer G, Maher L, Lloyd AR, Hellard M, Prins M, Dore GJ, Page K, . Int J Epidemiol. 2013 Dec; 42(6): 1649-1659.

The International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC(3)) Study is an international multi-cohort project of pooled biological and behavioural data from nine prospective cohorts of people who inject drugs (PWID). InC(3) brings together researchers from Australia, Canada, USA and the Netherlands with expertise in epidemiology, biostatistics, clinical and behavioural sciences, virology and immunology to investigate research questions relevant to hepatitis C virus (HCV) and HIV outcomes. InC(3) was established to: (i) create a merged multi-cohort study of pooled data from well-characterized cohorts of PWID with prospective data on HIV and HCV infections, with a particular focus on HCV; (ii) facilitate new studies not possible within individual cohorts; and (iii) bring together researchers across disciplines to answer a broad range of research questions. Study cohorts identify acute HCV cases through follow-up of high-risk HCV antibody-negative PWID or through clinical referral networks. To date, data from 1986 to 2010 have been received from all contributing cohorts, with 821 HCV-infected and 1216 HCV-uninfected participants (overall, n = 2037). Data collected include demographics, host genetics, HCV ribonucleic acid testing, alanine aminotransferase testing, HIV/hepatitis B virus testing, HCV therapy, loss to follow-up and mortality.

**Impact Of Hepatitis Coinfection On Hospitalization Rates and Causes In A Multicenter Cohort Of Persons Living With HIV** Crowell TA, Gebo KA, Balagopal A, Fleishman JA, Agwu AL, Berry SA, . J Acquir Immune Defic Syndr. 2014 Apr; 65(4): 429-437.

Chronic viral hepatitis is a potentially important determinant of health care utilization among persons living with HIV. The authors describe hospitalization rates and reasons for hospitalization among persons living with HIV stratified by coinfection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV). Laboratory, demographic, and hospitalization data were obtained for all patients receiving longitudinal HIV care during 2010 at 9 geographically diverse sites. Hepatitis serostatus was assessed by hepatitis B surface antigen and/or hepatitis C antibody. ICD-9 codes were used to assign hospitalizations into diagnostic categories. Negative binomial regression was used to assess factors associated with all-cause and diagnostic category-specific hospitalizations. A total of 2793



hospitalizations were observed among 12,819 patients. Of these patients, 49.3% had HIV monoinfection, 4.1% HIV/HBV, 15.4% HIV/HCV, 2.5% HIV/HBV/HCV, and 28.7% unknown hepatitis serostatus. Compared with HIV monoinfection, the risk of all-cause hospitalization was increased with HIV/HBV [adjusted incidence rate ratio 1.55 (1.17 to 2.06)], HIV/HCV [1.45 (1.21 to 1.74)], and HIV/HBV/HCV [1.52 (1.04 to 2.22)]. Risk of hospitalization for non-AIDS-defining infection was also higher among patients with HIV/HBV [2.07 (1.38 to 3.11)], HIV/HCV [1.81 (1.36 to 2.40)], and HIV/HBV/HCV [1.96 (1.11 to 3.46)]. HIV/HBV was associated with hospitalization for gastrointestinal/liver disease [2.55 (1.30 to 5.01)]. HIV/HCV was associated with hospitalization for psychiatric illness [1.89 (1.11 to 3.26)]. HBV and HCV coinfection are associated with increased risk of all-cause hospitalization and hospitalization for non-AIDS-defining infections, as compared with HIV monoinfection. Policy-makers and third-party payers should be aware of the heightened risk of hospitalization associated with coinfection when allocating health care resources and considering models of health care delivery.

### **Use Of Laser Capture Microdissection To Map Hepatitis C Virus-Positive Hepatocytes In**

**Human Liver** Kandathil AJ, Graw F, Quinn J, Hwang HS, Torbenson M, Perelson AS, Ray SC, Thomas DL, Ribeiro RM, Balagopal A. *Gastroenterology*. 2013 Dec; 145(6): 1404-1413. e1-10. Hepatitis C virus (HCV) predominantly infects hepatocytes, but many hepatocytes are not infected; studies have shown that HCV antigens cluster within the liver. The authors investigated spatial distribution and determinants of HCV replication in human liver samples. They analyzed liver samples from 4 patients with chronic HCV infection (genotype 1, Metavir scores 0-1) to estimate the proportion of infected hepatocytes and the amount of HCV viral RNA (vRNA) per cell. Single-cell laser capture microdissection was used to capture more than 1000 hepatocytes in grids, to preserve geometric relationships. HCV vRNA and interferon-induced transmembrane protein 3 (IFITM3) messenger RNA (the transcript of an interferon-stimulated gene) were measured in the same hepatocytes by quantitative polymerase chain reaction and assembled in maps to identify areas of high and low HCV replication. Patients' serum levels of HCV RNA ranged from 6.87 to 7.40 log<sub>10</sub> IU/mL; the proportion of HCV-infected hepatocytes per person ranged from 21% to 45%, and the level of vRNA ranged from 1 to 50 IU/hepatocyte. Infection was not random; the authors identified clustering of HCV-positive hepatocytes using infected-neighbor analysis ( $P < .0005$ ) and distance to the  $k$ th nearest neighbor compared with random distributions, obtained by bootstrap simulations ( $P < .02$ ). Hepatocytes that expressed IFITM3 did not appear to cluster and were largely HCV negative. They used single-cell laser capture and high-resolution analysis to show that in human liver HCV infects hepatocytes in nonrandom clusters, whereas expression of antiviral molecules is scattered among hepatocytes. These findings show that quantitative single-cell RNA measurements can be used to estimate the abundance of HCV vRNA per infected human hepatocyte and are consistent with cell-cell propagation of infection in the absence of clustered IFITM3.

### **Hepatitis C Virus Infection Is Not An Independent Risk Factor For Obstructive Lung Disease**

Fischer WA, Drummond MB, Merlo CA, Thomas DL, Brown R, Mehta SH, Wise RA, Kirk GD. *COPD*. 2014 Feb; 11(1): 41918.

Several epidemiological studies have suggested that hepatitis C virus (HCV) infection is associated with the presence of obstructive lung disease (OLD). However, there is a strong link between HCV infection and tobacco abuse, a major risk factor for the development of OLD. In this study the authors analyzed clinical, laboratory and spirometric data from 1068 study participants to assess whether HCV infection, viremia, or HCV-associated end organ damage were associated with OLD. Demographics, risk behavior, serologic status for HCV and HIV, and spirometric measurements were collected from a cross-sectional analysis of the Acquired Immunodeficiency Syndrome (AIDS) Linked to the

IntraVenous Experience (ALIVE) study, an observational cohort of IDUs followed in Baltimore, MD since 1988. Of 1,068 participants, 890 (83%) were HCV positive and 174 (16%) met spirometric criteria for OLD. Factors independently associated with OLD were age and BMI. HCV infection, viral load and HCV-associated end organ damage were similar in participants with and without OLD. In summary, there was no independent association between markers of HCV exposure, chronicity, viremia, or HCV-associated end-organ damage with OLD. These findings support the strong correlation between HCV status, injection drug use, and smoking. These data suggest that HCV may not be a sole contributor to the increased prevalence of OLD described in previous studies of HCV-infected individuals.

### **Effect Of Fibrosis On Adverse Events In Patients With Hepatitis C Treated With Telaprevir**

Bichoupan K, Schwartz JM, Martel-Laferriere V, Giannattasio ER, Marfo K, Odin JA, Liu LU, Schiano TD, Perumalswami P, Bansal M, Gaglio PJ, Kalia H, Dieterich DT, Branch AD, Reinus JF. *Aliment Pharmacol Ther.* 2014 Jan; 39(2): 209-216.

Data about adverse events are needed to optimise telaprevir-based therapy in a broad spectrum of patients. To investigate adverse events of telaprevir-based therapy in patients with and without advanced fibrosis or cirrhosis in a real-world setting. Data on 174 hepatitis C-infected patients initiating telaprevir-based therapy at Mount Sinai and Montefiore medical centres were collected. Biopsy data and FIB-4 scores identified patients with advanced fibrosis. Multivariable fully adjusted models were built to assess the effect of advanced fibrosis on specific adverse events and discontinuation of treatment due to an adverse event. Patients with (n = 71) and without (n = 103) advanced fibrosis were similar in BMI, ribavirin exposure, gender, prior treatment history, haemoglobin and creatinine, but differed in race. Overall, 47% of patients completed treatment and 40% of patients achieved SVR. Treated patients with and without advanced fibrosis or cirrhosis had similar rates of adverse events; advanced fibrosis, however, was independently associated with anorectal discomfort (P = 0.03). Three patients decompensated and had advanced fibrosis. The discontinuation of all treatment medications due to an adverse event was significantly associated with older age (P = 0.01), female gender (P = 0.01) and lower platelets (P = 0.03). Adverse events were common, but were not significantly related to the presence of advanced fibrosis or cirrhosis. More critical monitoring in older and female patients with low platelets throughout treatment may reduce adverse event-related discontinuations.

### **Virological Response Rates For Telaprevir-Based Hepatitis C Triple Therapy In Patients With and Without HIV Coinfection**

Martel-Laferrière V, Brinkley S, Bichoupan K, Posner S, Stivala A, Perumalswami P, Schiano T, Sulkowski M, Dieterich D, Branch A. *HIV Med.* 2014 Feb; 15(2): 108-115.

Pegylated-interferon/ribavirin dual therapy for hepatitis C virus (HCV) infection has a lower sustained virological response (SVR) rate in HIV/HCV-coinfected patients than in HCV monoinfected patients, but little is known about the relative effectiveness of teleprevir-based triple therapy in the two groups. Data on 33 coinfectd and 116 monoinfected patients were analysed on an intention-to-treat basis. SVR12 was defined as undetectable HCV RNA at week 12 post-end-of-treatment, severe anaemia as haemoglobin  $\leq 89$ g/L or a drop of  $\geq 45$ g/L, and advanced fibrosis/cirrhosis as Fib-4  $\geq 3.25$ . All coinfectd patients had well controlled HIV infection. The groups were similar in age, gender, percentage with Fib-4  $\geq 3.25$  and HCV viral load, but differed in previous treatment response, with more coinfectd patients being nonresponders or treatment-intolerant (75.8% vs. 50.0% for monoinfected patients; P<0.01). During treatment, the percentages of patients with undetectable HCV RNA were similar, but, surprisingly, this percentage tended to be higher in coinfectd patients. SVR12 rates were 60.6% in coinfectd patients vs. 42.2% in monoinfected patients (P=0.06). In

multivariable analysis, SVR12 was associated with HIV infection [odds ratio (OR) 3.55;  $P < 0.01$ ], African American race (OR 0.37;  $P = 0.03$ ) and previous treatment response (OR 0.46;  $P = 0.03$ ). Rates of severe anaemia (45.5 vs. 58.6% in coinfecting and mono-infected patients, respectively;  $P = 0.18$ ) were similar in the two groups, but rash (15.2 vs. 34.5%, respectively;  $P = 0.03$ ) and rectal symptoms (12.1 vs. 43.1%, respectively;  $P < 0.01$ ) were less common in coinfecting patients. Virological responses of coinfecting and mono-infected patients did not differ significantly, but tended to be higher in coinfecting patients, who had a 60.6% SVR12 rate. Telaprevir-based triple therapy is a promising option for coinfecting patients with well-controlled HIV infection.

#### **Evaluation Of Hepatitis C Virus As A Risk Factor For HIV-Associated Neuroretinal Disorder**

Branch AD, Drye LT, Van Natta ML, Sezgin E, Fishman SL, Dieterich DT, Meinert CL, Jabs DA. Clin Infect Dis. 2013 Dec; 57(11): 1618-1625.

Both hepatitis C virus (HCV) and human immunodeficiency virus (HIV) penetrate the central nervous system. HIV-associated neuroretinal disorder (HIV-NRD), a visual impairment of reduced contrast sensitivity and reading ability, is associated with cytokine dysregulation and genetic polymorphisms in the anti-inflammatory interleukin 10 (IL-10) signaling pathway. The authors investigated associations between HCV and HIV-NRD and between HCV and single-nucleotide polymorphisms (SNPs) in the IL-10 receptor 1 (IL10R1) gene. Logistic and Cox regression analysis were used to analyze risk factors for HIV-NRD in 1576 HIV-positive patients who did not have an ocular opportunistic infection at enrollment. Median follow-up was 4.9 years (interquartile range, 2.4-8.8 years). Four IL10R1 SNPs were examined in a subset of 902 patients. The group included 290 patients with chronic HCV infection, 74 with prior infection, and 1212 with no HCV markers. There were 244 prevalent cases of HIV-NRD and 263 incident cases (rate = 3.9/100 person-years). In models adjusted for demographics, HIV treatment and status, liver function, and immune status, both the prevalence and incidence of HIV-NRD were significantly higher in patients with chronic HCV infection (odds ratio = 1.54; 95% confidence interval [CI], 1.03-2.31 and hazard ratio = 1.62; 95% CI, 1.13-2.34, respectively), compared to patients with no HCV markers. Chronic HCV was associated with rs2228055 and 2 additional IL-10R1 SNPs expected to reduce IL-10 signaling. HIV-NRD was not significantly associated with these SNPs. HCV is a possible risk factor for HIV-NRD. Genetic analysis suggests that alterations in the IL-10 signaling pathway may increase susceptibility to HIV-NRD and HCV infection. Inflammation may link HCV and HIV-NRD.

#### **Variants In HAVCR1 Gene Region Contribute To Hepatitis C Persistence In African Americans**

Wojcik G, Latanich R, Mosbruger T, Astemborski J, Kirk GD, Mehta SH, Goedert JJ, Kim AY, Seaberg EC, Busch M, Thomas DL, Duggal P, Thio CL. J Infect Dis. 2014 Feb; 209(3): 355-359. To confirm previously identified polymorphisms in HAVCR1 that were associated with persistent hepatitis C virus (HCV) infection in individuals of African and of European descent, the authors studied 165 subjects of African descent and 635 subjects of European descent. Because the association was only confirmed in subjects of African descent (rs6880859; odds ratio, 2.42;  $P = .01$ ), they then used 379 subjects of African descent (142 with spontaneous HCV clearance) to fine-map HAVCR1. rs111511318 was strongly associated with HCV persistence after adjusting for IL28B and HLA (adjusted  $P = 8.8 \times 10^{-4}$ ), as was one 81-kb haplotype (adjusted  $P = .0006$ ). The HAVCR1 genomic region is an independent genetic determinant of HCV persistence in individuals of African descent.

#### **Association Of The IFNL4-ΔG Allele With Impaired Spontaneous Clearance Of Hepatitis C Virus**

Aka PV, Kuniholm MH, Pfeiffer RM, Wang AS, Tang W, Chen S, Astemborski J, Plankey M, Villacres MC, Peters MG, Desai S, Seaberg EC, Edlin BR, Strickler HD, Thomas DL, Prokunina-Olsson L, Sharp GB, O'Brien TR. J Infect Dis. 2014 Feb; 209(3): 350-354.

Interferon lambda 4 protein can be generated in IFNL4-ΔG carriers but not IFNL4-TT homozygotes. The authors studied 890 anti-hepatitis C virus (HCV)-positive participants in the Women's Interagency HIV Study. Among blacks (n = 555), HCV was more often cleared for those with genotype IFNL4-TT/TT (32. 6%; odds ratio [OR], 3.59; P =  $3.3 \times 10^{-5}$ ) than IFNL4-TT/ΔG (11. 3%; OR, 0.95; P = .86) or IFNL4-ΔG/ΔG (11.9%; referent). Pooling these data with published results in blacks (n = 1678), ORs were 3.84 (P =  $8.6 \times 10^{-14}$ ) for IFNL4-TT/TT and 1. 44 (P = .03) IFNL4-TT/ΔG, and the area under the curve was 0.64 for IFNL4-ΔG genotype and 0.61 for rs12979860 (IL28B). IFNL4-ΔG is strongly associated with impaired spontaneous HCV clearance.

**The Effects Of Female Sex, Viral Genotype, and IL28B Genotype On Spontaneous Clearance Of Acute Hepatitis C Virus Infection** Grebely J, Page K, Sacks-Davis R, van der Loeff MS, Rice TM, Bruneau J, Morris MD, Hajarizadeh B, Amin J, Cox AL, Kim AY, McGovern BH, Schinkel J, George J, Shoukry NH, Lauer GM, Maher L, Lloyd AR, Hellard M, Dore GJ, Prins M. Hepatology 2014 Jan; 59(1): 109-120.

Although 20%-40% of persons with acute hepatitis C virus (HCV) infection demonstrate spontaneous clearance, the time course and factors associated with clearance remain poorly understood. The authors investigated the time to spontaneous clearance and predictors among participants with acute HCV using Cox proportional hazards analyses. Data for this analysis were drawn from an international collaboration of nine prospective cohorts evaluating outcomes after acute HCV infection. Among 632 participants with acute HCV, 35% were female, 82% were Caucasian, 49% had interleukin-28 (IL28)B CC genotype (rs12979860), 96% had injected drugs ever, 47% were infected with HCV genotype 1, and 7% had human immunodeficiency virus (HIV) coinfection. Twenty-eight percent were HCV antibody negative/RNA positive at the time of acute HCV detection (early acute HCV). During follow-up, spontaneous clearance occurred in 173 of 632, and at 1 year after infection, 25% (95% confidence interval [CI] 21, 29) had cleared virus. Among those with clearance, the median time to clearance was 16. 5 weeks (IQR: 10. 5, 33. 4), with 34%, 67%, and 83% demonstrating clearance at 3, 6, and 12 months. Adjusting for age, factors independently associated with time to spontaneous clearance included female sex (adjusted hazards ratio [AHR] 2.16; 95% CI: 1.48, 3.18), IL28B CC genotype (versus CT/TT; AHR, 2. 26; 95% CI: 1.52, 3.34), and HCV genotype 1 (versus non-genotype 1; AHR: 1. 56; 95% CI: 1. 06, 2.30). The effect of IL28B genotype and HCV genotype on spontaneous clearance was greater among females, compared to males. Female sex, favorable IL28B genotype, and HCV genotype 1 are independent predictors of spontaneous clearance. Further research is required to elucidate the observed sex-based differences in HCV control.

**All-Oral Combination Of Ledipasvir, Velpatasvir, Tegobuvir, and Ribavirin In Treatment-Naive Patients With Genotype 1 HCV Infection** Wyles DL, Rodriguez-Torres M, Lawitz E, Shiffman ML, Pol S, Herring RW, Massetto B, Kanwar B, Trenkle JD, Pang PS, Zhu Y, Mo H, Brainard DM, Subramanian GM, McHutchison JG, Habersetzer F, Sulkowski MS. Hepatology. 2014 Feb; [Epub ahead of print].

This phase 2 trial assessed the efficacy and safety of a combination regimen of the NS5A inhibitor ledipasvir (LDV), NS3 protease inhibitor velpatasvir (VDP), nonnucleoside NS5B inhibitor tegobuvir (TGV), and ribavirin (RBV) in treatment-naive patients with chronic hepatitis C virus (HCV) genotype 1 without cirrhosis. Patients were randomized 1:2 to LDV 30 mg once daily (QD) (Arm 1; n = 46) or LDV 90 mg QD (Arm 2; n = 94); patients in both arms also received VDP 200 mg QD, TGV 30 mg twice daily, and RBV 1000-1200 mg/day. Patients in Arm 2 with vRVR, defined as HCV RNA <LLOQ from treatment weeks 2-10, were randomized 1:1 to stop treatment at 12 weeks or continue for 24 weeks. Sustained virologic response 12 weeks after treatment (SVR12) was higher in patients receiving 90 mg LDV for 24 weeks (63%) compared to LDV 90 mg for 12 weeks (54%) and LDV 30

mg for 24 weeks (48%). In patients with vRVR in Arm 2, SVR12 was achieved by 68% and 81% of patients treated for 12 and 24 weeks, respectively. Virologic breakthrough was more common in patients with HCV genotype 1a and was associated with resistance-associated variants for all three direct-acting antiviral agents (DAAs); however, in all but 1 patient who relapsed, RAVs directed against only one or two of the DAAs were detected. The most common adverse events were fatigue, headache, nausea, rash, and diarrhea. In patients with HCV genotype 1, an interferon-free regimen containing LDV/VDV/TGV/RBV was well tolerated and led to SVR12 in up to 63% of patients. LDV 90 mg is currently being investigated in combination with the nucleotide polymerase inhibitor sofosbuvir.

**Fibrosis Progression In Human Immunodeficiency Virus/Hepatitis C Virus Coinfected Adults: Prospective Analysis Of 435 Liver Biopsy Pairs** Konerman MA, Mehta SH, Sutcliffe CG, Vu T, Higgins Y, Torbenson MS, Moore RD, Thomas DL, Sulkowski MS. *Hepatology*. 2014 Mar; 59(3): 767-775.

Human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfection is associated with progressive liver disease. However, the rate of progression is variable and the ability to differentiate patients with stable versus progressive HCV disease is limited. The objective of this study was to assess the incidence of and risk factors for fibrosis progression in a prospective cohort of coinfecting patients. Overall, 435 liver biopsy pairs from 282 patients without cirrhosis were analyzed. Biopsies were scored according to the METAVIR system by a single pathologist blind to biopsy sequence. Fibrosis progression was defined as an increase of at least one METAVIR fibrosis stage between paired biopsies. The majority of patients were African American (84.8%), male (67.7%), and infected with HCV genotype 1 (93.4%). On initial biopsy, no or minimal fibrosis was identified in 243 patients (86%). The median interval between biopsies was 2.5 years. Fibrosis progression was observed in 97 of 282 (34%) patients and 149 of 435 (34%) biopsy pairs. After adjustment, greater body mass index (adjusted odds ratio [aOR] 1.04 per 1 unit increase), diabetes (aOR: 1.56), and hepatic steatosis (aOR: 1.78) at the time of initial biopsy were marginally associated with subsequent fibrosis progression. Between biopsies, elevated serum aspartate and alanine aminotransferase (AST, ALT) (aOR AST: 3.34, ALT: 2.18 for >25% values >100 U/L versus <25% values >100 U/L) were strongly associated with fibrosis progression. Fibrosis progression is common among HIV/HCV coinfecting patients; these data suggest that progression can be rapid. Persistent elevations in serum transaminase levels may serve as important noninvasive markers to identify subsets of patients who are more likely to progress and thus warrant closer monitoring and consideration of HCV treatment.

**Phase 2B Trial Of Interferon-Free Therapy For Hepatitis C Virus Genotype 1** Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, Everson GT, Kwo P, Foster GR, Sulkowski MS, Xie W, Pilot-Matias T, Liou G, Larsen L, Khatri A, Podsadecki T, Bernstein B. *N Engl J Med*. 2014 Jan; 370(3): 222-232.

An interferon-free combination of the protease inhibitor ABT-450 with ritonavir (ABT-450/r), the nonnucleoside polymerase inhibitor ABT-333, and ribavirin showed efficacy against the hepatitis C virus (HCV) in a pilot study involving patients with HCV genotype 1 infection. The addition of another potent agent, the NS5A inhibitor ABT-267, may improve efficacy, especially in difficult-to-treat patients. This study was designed to evaluate multiple regimens of direct-acting antiviral agents and ribavirin in patients with HCV genotype 1 infection who had not received therapy previously or who had no response to prior therapy with pegylated interferon and ribavirin. In this phase 2b, open-label study with 14 treatment subgroups, 571 patients without cirrhosis who had not received treatment previously or who had not had a response to prior therapy were randomly assigned to a regimen of ABT-450/r, combined with ABT-267 or ABT-333 or both, for 8, 12, or 24 weeks and received at least

one dose of therapy. All the subgroups but 1 also received ribavirin (dose determined according to body weight). The primary end point was sustained virologic response at 24 weeks after the end of treatment. The primary efficacy analysis compared rates between previously untreated patients who received three direct-acting antiviral agents and ribavirin for 8 weeks and those who received the same therapy for 12 weeks. Among previously untreated patients who received three direct-acting antiviral agents (with the ABT-450/r dose administered as 150 mg of ABT-450 and 100 mg of ritonavir) plus ribavirin, the rate of sustained virologic response at 24 weeks after treatment was 88% among those who received the therapy for 8 weeks and 95% among those who received the therapy for 12 weeks (difference, -7 percentage points; 95% confidence interval, -19 to 5; P=0.24). The rates of sustained virologic response across all treatment subgroups ranged from 83 to 100%. The most frequent adverse events were fatigue, headache, nausea, and insomnia. Eight patients (1%) discontinued treatment owing to adverse events. In this phase 2b study, all-oral regimens of antiviral agents and ribavirin were effective both in patients with HCV genotype 1 infection who had not received therapy previously and in those who had not had a response to prior therapy. (Funded by AbbVie; ClinicalTrials.gov number, NCT01464827).

### **Daclatasvir Plus Sofosbuvir For Previously Treated Or Untreated Chronic HCV Infection**

Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasele DM, . N Engl J Med. 2014 Jan; 370(3): 211-221.

All-oral combination therapy is desirable for patients with chronic hepatitis C virus (HCV) infection. The authors evaluated daclatasvir (an HCV NS5A replication complex inhibitor) plus sofosbuvir (a nucleotide analogue HCV NS5B polymerase inhibitor) in patients infected with HCV genotype 1, 2, or 3. In this open-label study, they initially randomly assigned 44 previously untreated patients with HCV genotype 1 infection and 44 patients infected with HCV genotype 2 or 3 to daclatasvir at a dose of 60 mg orally once daily plus sofosbuvir at a dose of 400 mg orally once daily, with or without ribavirin, for 24 weeks. The study was expanded to include 123 additional patients with genotype 1 infection who were randomly assigned to daclatasvir plus sofosbuvir, with or without ribavirin, for 12 weeks (82 previously untreated patients) or 24 weeks (41 patients who had previous virologic failure with telaprevir or boceprevir plus peginterferon alfa-ribavirin). The primary end point was a sustained virologic response (an HCV RNA level of <25 IU per milliliter) at week 12 after the end of therapy. Overall, 211 patients received treatment. Among patients with genotype 1 infection, 98% of 126 previously untreated patients and 98% of 41 patients who did not have a sustained virologic response with HCV protease inhibitors had a sustained virologic response at week 12 after the end of therapy. A total of 92% of 26 patients with genotype 2 infection and 89% of 18 patients with genotype 3 infection had a sustained virologic response at week 12. High rates of sustained virologic response at week 12 were observed among patients with HCV subtypes 1a and 1b (98% and 100%, respectively) and those with CC and non-CC IL28B genotypes (93% and 98%, respectively), as well as among patients who received ribavirin and those who did not (94% and 98%, respectively). The most common adverse events were fatigue, headache, and nausea. Once-daily oral daclatasvir plus sofosbuvir was associated with high rates of sustained virologic response among patients infected with HCV genotype 1, 2, or 3, including patients with no response to prior therapy with telaprevir or boceprevir. (Funded by Bristol-Myers Squibb and Pharmasset (Gilead); A1444040 ClinicalTrials.gov number, NCT01359644. ).

**Infections During Peginterferon/Ribavirin Therapy Are Associated With The Magnitude Of Decline In Absolute Lymphocyte Count: Results Of The Ideal Study** Melia MT, Bräu N, Poordad F, Lawitz EJ, Shiffman ML, McHutchison JG, Muir AJ, Galler GW, Nyberg LM, Lee WM, Schiff E, Long J, Noviello S, Brass CA, Pedicone LD, Sulkowski MS. Clin Infect Dis. 2014 Apr; 58(7): 960-969.

Myelosuppression due to pegylated interferon (peg-IFN) is common during treatment for hepatitis C virus. The relationship between infection risk and decreases in leukocyte lines, however, is not well established. The objective of this analysis was to determine the incidence of and risk factors for infections during peg-IFN/ribavirin (RBV) therapy. A total of 3070 treatment-naïve, chronic hepatitis C genotype 1-infected patients were treated for up to 48 weeks with peg-IFN alfa-2b 1.5 µg/kg/week or 1 µg/kg/week, or peg-IFN alfa-2a 180 µg/week plus RBV. On-treatment leukocyte counts were obtained every 2-6 weeks. Dose reduction was required for a neutrophil count  $<0.75 \times 10^9$  cells/L, and treatment discontinuation was required for a neutrophil count  $<0.5 \times 10^9$  cells/L. Granulocyte colony-stimulating factor was prohibited. Data on infections were captured at each study visit and categorized according to MedDRA version 13.0. A total of 581 (19%) patients experienced moderate, severe, or life-threatening infections as assessed by the investigator; 648 (21%) patients had at least 1 neutrophil count  $<0.75 \times 10^9$  cells/L, but only 242 (8%) sustained an infection and had a neutrophil count  $<0.75 \times 10^9$  cells/L at any time while on treatment. Twelve patients had severe or life-threatening infection and grade 3/4 neutropenia, but only 4 had temporally related infections. In a multivariate logistic regression model, nadir lymphocyte count, history of depression, and female sex, but not nadir neutrophil count, were associated with moderate, severe, or life-threatening infection. Nadir lymphocyte count, not nadir neutrophil count, was independently associated with moderate, severe, or life-threatening infections in the IDEAL study. Clinicians should be aware of their patients' absolute lymphocyte counts during peg-IFN/RBV therapy; peg-IFN dose reductions may be a consideration in patients with significant lymphocytopenia ( $<0.5 \times 10^9$  cells/L).

**Significance Of Lipid Composition In A Blood-Brain Barrier-Mimetic Pampa Assay** Campbell SD, Regina KJ, Kharasch ED. J Biomol Screen. 2014 Mar; 19(3): 437-444.

Endothelial cells forming the blood-brain barrier limit drug access into the brain, due to tight junctions, membrane drug transporters, and unique lipid composition. Passive permeability, thought to mediate drug access, is typically tested using porcine whole-brain lipid. However, human endothelial cell lipid composition differs. This investigation evaluated the influence of lipid composition on passive permeability across artificial membranes. Permeability of CNS-active drugs across an immobilized lipid membrane was determined using three lipid models: crude extract from whole pig brain, human brain microvessel lipid, and microvessel lipid plus cholesterol. Lipids were immobilized on polyvinylidene difluoride, forming donor and receiver chambers, in which drug concentrations were measured after 2 h. The log of effective permeability was then calculated using the measured concentrations. Permeability of small, neutral compounds was unaffected by lipid composition. Several structurally diverse drugs were highly permeable in porcine whole-brain lipid but one to two orders of magnitude less permeable across human brain endothelial cell lipid. Inclusion of cholesterol had the greatest influence on bulky amphipathic compounds such as glucuronide conjugates. Lipid composition markedly influences passive permeability. This was most apparent for charged or bulky compounds. These results demonstrate the importance of using species-specific lipid models in passive permeability assays.

**Enhanced Blood-Brain Barrier Transmigration Using A Novel Transferrin Embedded Fluorescent Magneto-Liposome Nanoformulation** Ding H, Sagar V, Agudelo M, Pilakka-Kanthikeel S, Atluri VS, Raymond A, Samikkannu T, Nair MP. Nanotechnology. 2014 Feb; 25(5): 55101.

The blood-brain barrier (BBB) is considered as the primary impediment barrier for most drugs. Delivering therapeutic agents to the brain is still a big challenge to date. In this study, a dual mechanism, receptor mediation combined with external non-invasive magnetic force, was incorporated into ferrous magnet-based liposomes for BBB transmigration enhancement. The homogenous magnetic nanoparticles (MNPs), with a size of  $\sim 10$  nm, were synthesized and confirmed by TEM and XRD respectively. The classical magnetism assay showed the presence of the characteristic superparamagnetic property. These MNPs encapsulated in PEGylated fluorescent liposomes as magneto-liposomes (MLs) showed mono-dispersion,  $\sim 130 \pm 10$  nm diameter, by dynamic laser scattering (DLS) using the lipid-extrusion technique. Remarkably, a magnetite encapsulation efficiency of nearly 60% was achieved. Moreover, the luminescence and hydrodynamic size of the MLs was stable for over two months at  $4^\circ\text{C}$ . Additionally, the integrity of the ML structure remained unaffected through 120 rounds of circulation mimicking human blood fluid. After biocompatibility confirmation by cytotoxicity evaluation, these fluorescent MLs were further embedded with transferrin and applied to an in vitro BBB transmigration study in the presence or absence of external magnetic force. Comparing with magnetic force- or transferrin receptor-mediated transportation alone, their synergy resulted in 50-100% increased transmigration without affecting the BBB integrity. Consequently, confocal microscopy and iron concentration in BBB-composed cells further confirmed the higher cellular uptake of ML particles due to the synergic effect. Thus, our multifunctional liposomal magnetic nanocarriers possess great potential in particle transmigration across the BBB and may have a bright future in drug delivery to the brain.



## **SERVICES RESEARCH**

**Reducing Risky Relationships: A Multisite Randomized Trial of a Prison-Based Intervention for Reducing HIV Sexual Risk Behaviors among Women with a History of Drug Use** Knudsen HK, Staton-Tindall M, Oser CB, Havens JR, Leukefeld CG. AIDS Care. 2014 Jan 13 [e-pub ahead of print].

Women involved in the criminal justice system, particularly those with a history of drug use, are at elevated risk of HIV infection, yet few HIV prevention interventions have been tailored for delivery to incarcerated women. Drawing on the Relational Model, the Reducing Risky Relationships for HIV (RRR-HIV) intervention was developed and evaluated in a multisite randomized clinical trial. Women with weekly drug use prior to incarceration (n = 444) who were incarcerated within correctional institutions in four states were randomized to (1) the RRR-HIV intervention consisting of an HIV educational video, five group sessions, and one post-release booster session or (2) a control condition consisting of the HIV educational video. The RRR-HIV intervention combined didactic and interactive content regarding seven "thinking myths" about intimate relationships that may result in decisions to engage in risky sexual behaviors. Data were collected while women were still incarcerated and approximately 90 days following release from prison by trained interviewers. A negative binomial regression (NBR) model of unprotected sexual behaviors at the 90-day follow-up indicated that RRR-HIV participants reported fewer unprotected sexual behaviors than women in the control condition once the analysis was adjusted for study site. Future studies should examine the sustainability of the RRR-HIV intervention's effect on risk reduction. Implementation research is needed to determine whether delivery of this intervention by correctional staff or peers, rather than research staff, yields similar reductions in unprotected sexual behaviors.

**Gender Disparities in HIV Treatment Outcomes Following Release from Jail: Results from a Multicenter Study** Meyer JP, Zelenev A, Wichersham J, Williams C, Teixeira P, Altice F. Am J Public Health. 2014; 104: 434–441. doi: 10.2105/AJPH.2013.301553.

The authors assessed gender differences in longitudinal HIV treatment outcomes among HIV-infected jail detainees transitioning to the community. Data were from the largest multisite prospective cohort study of HIV-infected released jail detainees (n = 1270)-the Enhancing Linkages to HIV Primary Care and Services in Jail Setting Initiative, January 2008 and March 2011, which had 10 sites in 9 states. The authors assessed baseline and 6-month HIV treatment outcomes, stratifying by gender. Of 867 evaluable participants, 277 (31.9%) were women. Compared with men, women were more likely to be younger, non-Hispanic White, married, homeless, and depressed, but were similar in recent alcohol and heroin use. By 6 months post-release, women were significantly less likely than men to experience optimal HIV treatment outcomes, including (1) retention in care (50% vs 63%), (2) antiretroviral therapy prescription (39% vs 58%) or optimal antiretroviral therapy adherence (28% vs 44%), and (3) viral suppression (18% vs 30%). In multiple logistic regression models, women were half as likely as men to achieve viral suppression. HIV-infected women transitioning from jail experience greater comorbidity and worse HIV treatment outcomes than men. Future interventions that transition people from jail to community-based HIV clinical care should be gender-specific.

**Addiction Treatment Centers' Progress in Preparing for Health Care Reform** Molfente TD. J Subst Abuse Treat. 2014; 46(2): 158-164.

The Patient Protection and Affordable Care Act (PPACA) is expected to significantly alter addiction treatment service delivery. Researchers designed the Health Reform Readiness Index (HRRI) for addiction treatment organizations to assess their readiness for the PPACA. Four-hundred twenty-seven organizations completed the HRRI throughout a 3-year period, using a four-point scale to rank their

readiness on 13 conditions. HRRI results completed during two different time periods (between 10/1/2010-6/30/2011 and 9/1/2011-9/30/2012) were analyzed and compared. Most respondents self-assessed as being in the early stages of preparation for 9 of the 13 conditions. Survey results showed that organizations with annual budgets <\$5 million (n=295) were less likely to be prepared for the PPACA than organizations with annual budgets >\$5 million (n=132). The HRRI results suggest that the addiction field, and in particular smaller organizations, is not preparing adequately for health care reform; organizations that are making preparations are making only modest gains.

**MAPIT: Development of a Web-Based Intervention Targeting Substance Abuse Treatment in the Criminal Justice System**

Walters ST, Ondersma SJ, Ingersoll KS, Rodriguez M, Lerch J, Rossheim ME, Taxman FS. J Subst Abuse Treat. 2014; 46(1): 60-65.

Although drug and alcohol treatment are common requirements in the U.S. criminal justice system, only a minority of clients actually initiate treatment. This paper describes a two-session, web-based intervention to increase motivation for substance abuse treatment among clients using illicit substances. MAPIT (Motivational Assessment Program to Initiate Treatment) integrates the extended parallel process model, motivational interviewing, and social cognitive theory. The first session (completed near the start of probation) targets motivation to complete probation, to make changes in substance use (including treatment initiation), and to obtain HIV testing and care. The second session (completed approximately 30 days after session 1) focuses on goal setting, coping strategies, and social support. Both sessions can generate emails or mobile texts to remind clients of their goals. MAPIT uses theory-based algorithms and a text-to-speech engine to deliver custom feedback and suggestions. In an initial test, participants indicated that the program was respectful, easy to use, and would be helpful in making changes in substance use. MAPIT is being tested in a randomized trial in two large U.S. probation agencies. MAPIT addresses the difficulties of many probation agencies to maximize client involvement in treatment, in a way that is cost effective and compatible with the existing service delivery system.

**Treating Substance Use Disorders in the Criminal Justice System** Belenko S, Hiller M, Hamilton L. Curr Psychiatry Rep. 2013; 15(11): 414.

The large number of individuals with substance use disorders involved in the nation's criminal justice system (CJS) represents a unique opportunity, as well as challenges, in addressing the dual concerns of public safety and public health. Unfortunately, a low proportion of those who could benefit from treatment actually receive it while involved in the CJS. This article presents a review of recent research on the effectiveness of major substance abuse treatment interventions used at different possible linkage points during criminal justice case processing, including diversion, jail, prison, and community supervision. This is followed by a discussion of key research and practice issues, including low rates of treatment access and under-utilization of medication-assisted treatment. Concluding comments discuss principles of effective treatment for offenders and identify key gaps in research and practice that need to be addressed to improve and expand provision of effective treatment for offenders.

**Methadone Treatment Improves Tuberculosis Treatment among Hospitalized Opioid Dependent Patients in Ukraine**

Morozova O, Dvoryak S, Altice FL. Int J Drug Policy. 2013; 24(6): e91-98.

Ukraine's volatile syndemics of tuberculosis (TB) and HIV among people who inject drugs (PWIDs) introduces numerous treatment challenges for each condition, including high mortality and development of multi-drug resistant TB (MDR-TB). A prospective, non-randomized 90-day observational study was conducted in six Ukrainian TB treatment sites to assess the effectiveness of integrating methadone maintenance (MMT) with TB treatment using: (1) 90-day TB treatment retention; (2) time to treatment discontinuation; (3) TB medication adherence; and (4) subject

disposition, including mortality. Of the 110 participants enrolled, 57 received MMT and 53 did not (non-MMT). All of the primary outcomes were significantly better in MMT versus non-MMT groups, including 90-day TB treatment completion (89.5% versus 73.6%;  $p=0.031$ ), time to TB treatment discontinuation ( $p=0.039$ ) and TB medication adherence (97.1% versus 86.2%;  $p<0.001$ ) after controlling for death. The major reasons for treatment non-completion in the non-MMT group included death ( $N=3$ ), administrative discharge from the clinic ( $N=5$ ), loss to follow-up ( $N=2$ ), and arrest ( $N=4$ ). Overall, 90-day mortality was high (8.2%). After controlling for covariates differing between the two groups at baseline, the only independent predictor of completing 90 days of TB treatment was receipt of MMT in an integrated treatment setting (AOR=3.05; 95% CI 1.08-8.66). MMT integrated into inpatient TB treatment significantly improves retention in TB treatment and TB medication adherence among PWIDs. These findings call for policy change to increase the number of MMT sites in TB facilities and make MMT a low-threshold treatment option for opioid dependence in Ukraine.

**Cost-Effectiveness Analysis of Recovery Management Checkups (RMC) for Adults with Chronic Substance Use Disorders: Evidence from a 4-Year Randomized Trial** McCollister KE, French MT, Freitas DM, Dennis ML, Scott CK, Funk RR. *Addiction*. 2013; 108(12): 2166-2174.

This study performs the first cost-effectiveness analysis (CEA) of Recovery Management Checkups (RMC) for adults with chronic substance use disorders. Cost-effectiveness analysis of a randomized clinical trial of RMC. Participants were assigned randomly to a control condition of outcome monitoring (OM-only) or the experimental condition OM-plus-RMC, with quarterly follow-up for 4 years. Participants were recruited from the largest central intake unit for substance abuse treatment in Chicago, Illinois, USA. A total of 446 participants who were 38 years old on average, 54% male, and predominantly African American (85%). Data on the quarterly cost per participant come from a previous study of OM and RMC intervention costs. Effectiveness is measured as the number of days of abstinence and number of substance use-related problems. Over the 4-year trial, OM-plus-RMC cost on average \$2184 more than OM-only ( $P < 0.01$ ). Participants in OM-plus-RMC averaged 1026 days abstinent and had 89 substance use-related problems. OM-only averaged 932 days abstinent and reported 126 substance use-related problems. Mean differences for both effectiveness measures were statistically significant ( $P < 0.01$ ). The incremental cost-effectiveness ratio for OM-plus-RMC was \$23.38 per day abstinent and \$59.51 per reduced substance-related problem. When additional costs to society were factored into the analysis, OM-plus-RMC was less costly and more effective than OM-only. Recovery Management Checkups are a cost-effective and potentially cost-saving strategy for promoting abstinence and reducing substance use-related problems among chronic substance users.

**Patterns of Homelessness and Implications for HIV Health after Release from Jail** Zelenev A, Marcus R, Kopelev A, Cruzado-Quinones J, Spaulding A, Desabrais M, Lincoln T, Altice FL. *AIDS Behav*. 2013; 17 Suppl 2: S181-194.

This empirical study examines the association between substance abuse, mental illness, health behaviors and different patterns of homelessness among recently released, HIV-infected jail detainees. Using longitudinal data from a 10-site study, the authors examine correlates of homelessness, transitions to and from stable housing and the effect of housing on HIV treatment outcomes. Based on their analysis, they found evidence that the transitions from homelessness are closely associated with a reduction in the use of alcohol and illicit drugs, a decline in drug addiction severity, and an improvement in mental health. In addition, they found evidence that disparities in the housing status contributed substantially to the observed gap in the HIV treatment outcomes between homeless and non-homeless patients, including in achievement of virological suppression over time.

**Partner Violence and Health among HIV-Infected Jail Detainees** Meyer JP, Wickersham JA, Fu JJ, Brown S-E, Sullivan, TP, Springer SA, Altice FL. Int J Prison Health. 2013; 9(3): 124-141.

Little is known about the association of intimate partner violence (IPV) with specific HIV treatment outcomes, especially among criminal justice (CJ) populations who are disproportionately affected by IPV, HIV, mental and substance use disorders (SUDs) and are at high risk of poor post-release continuity of care. Mixed methods were used to describe the prevalence, severity, and correlates of lifetime IPV exposure among HIV-infected jail detainees enrolled in a novel jail-release demonstration project in Connecticut. Additionally, the effect of IPV on HIV treatment outcomes and longitudinal healthcare utilization was examined. Structured baseline surveys defined 49% of 84 participants as having significant IPV-exposure, which was associated with female gender, longer duration since HIV diagnosis, suicidal ideation, having higher alcohol use severity, having experienced other forms of childhood and adulthood abuse, and homo/bisexual orientation. IPV was not directly correlated with HIV healthcare utilization or treatment outcomes. In-depth qualitative interviews with 20 surveyed participants, however, confirmed that IPV was associated with disengagement from HIV care especially in the context of overlapping vulnerabilities, including transitioning from CJ to community settings, having untreated mental disorders, and actively using drugs or alcohol at the time of incarceration. Post-release interventions for HIV-infected CJ populations should minimally integrate HIV secondary prevention with violence reduction and treatment for SUDs.

**Default Mode Network Activity in Male Adolescents with Conduct and Substance Use Disorder** Dalwani MS, Tregellas JR, Andrews-Hanna JR, Mikulich-Gilbertson SK, Raymond KM, Banich MT, Crowley TJ, Sakai JT. Drug Alcohol Depend. 2014; 134: 242-250.

Adolescents with conduct disorder (CD) and substance use disorders (SUD) experience difficulty evaluating and regulating their behavior in anticipation of future consequences. Given the role of the brain's default mode network (DMN) in self-reflection and future thought, this study investigates whether DMN is altered in adolescents with CD and SUD, relative to controls. Twenty adolescent males with CD and SUD and 20 male controls of similar ages underwent functional magnetic resonance imaging as they completed a risk-taking decision task. The authors used independent component analysis as a data-driven approach to identify the DMN spatial component in individual subjects. DMN activity was then compared between groups. Compared to controls, patients showed reduced activity in superior, medial and middle frontal gyrus (Brodmann area (BA) 10), retrosplenial cortex (BA 30) and lingual gyrus (BA 18), and bilateral middle temporal gyrus (BA 21/22) - DMN regions thought to support self-referential evaluation, memory, foresight, and perspective taking. Furthermore, this pattern of reduced activity in patients remained robust after adjusting for the effects of depression and attention-deficit hyperactivity disorder (ADHD). Conversely, when not adjusting for effects of depression and ADHD, patients demonstrated greater DMN activity than controls solely in the cuneus (BA 19). Collectively, these results suggest that comorbid CD and SUD in adolescents is characterized by atypical activity in brain regions thought to play an important role in introspective processing. These functional imbalances in brain networks may provide further insight into the neural underpinnings of conduct and substance use disorders.

**Concurrent Life-Course Trajectories of Employment and Marijuana-Use: Exploring Interdependence of Longitudinal Outcomes**

Hara M, Huang DY, Weiss RE, Hser Y-I. J Subst Abuse Treat. 2013; 45(5): 426-432.

This study analyzes data on 7661 individuals who participated in the 1979 National Longitudinal Survey of Youth (NLSY79) to estimate trajectories of employment and marijuana-use over a 17-year period. Bivariate random intercept and slope modeling is applied to examine concurrently the cross-correlation between the two concurrent longitudinal trajectories from age 23 to 39. Parameter estimates

indicate baseline level (at age 23) of employment to be negatively correlated with marijuana, suggesting marijuana-use is associated with lower workforce productivity at age 23. The longitudinal employment slope is positively correlated with employment intercept for both males and females, indicating that survey participants with higher levels of employment at age 23 are more likely to have a positive impact on employment trajectory over time. For males, however, the employment slope is also significantly correlated with marijuana intercept ( $r=-0.07$ ), indicating marijuana-use in early adulthood may uniquely lower workforce productivity over age.

**Optimizing Care for HIV-Infected People Who Use Drugs: Evidence-Based Approaches to Overcoming Healthcare Disparities**

Meyer JP, Althoff AL, Altice FL. Clin Infect Dis. 2013; 57(9): 1309-1317.

Substance use disorders (SUDs) and human immunodeficiency viruses (HIV) are pervasive epidemics that synergize, resulting in negative outcomes for HIV-infected people who use drugs (PWUDs). The expanding epidemiology of substance use demands a parallel evolution of the HIV specialist-beyond HIV to diagnosis and management of comorbid SUDs. The purpose of this paper is to describe healthcare disparities for HIV-infected PWUDs along each point of a continuum of care, and to suggest evidence-based strategies for overcoming these healthcare disparities. Despite extensive dedicated resources and availability of antiretroviral therapy (ART) in the United States, PWUDs continue to experience delayed HIV diagnosis, reduced entry into and retention in HIV care, delayed initiation of ART, and inferior HIV treatment outcomes. Overcoming these healthcare disparities requires integrated packages of clinical, pharmacological, behavioral, and social services, delivered in ways that are cost-effective and convenient and include, at a minimum, screening for and treatment of underlying SUDs.

**Cannabis Use Disorders are Comparatively Prevalent among Nonwhite Racial/Ethnic Groups and Adolescents: A National Study**

Wu L-T, Brady KT, Mannelli P, Killeen TK, NIDA PI Workgroup. J Psychiatr Res. 2014; 50: 26-35.

The racial/ethnic composition of the US population is shifting, with the nonwhite population growing faster than whites. The authors examined cannabis use disorder (CUD) prevalence's and correlate in seven racial/ethnic groups. They included cannabis use (CU) prevalence as a comparison. Data were from the 2005-2011 National Surveys on Drug Use and Health (N=394,400). Substance use among respondents aged 12+ years was assessed by computer-assisted, self-interviewing methods. The following were included as control variables: age, sex, family income, government assistance, county type, residential stability, major depressive episode history, arrest history, nicotine dependence, alcohol disorder, and survey year. Past-year CU prevalence increased significantly from 10.45% in 2005 to 11.41-11.54% during 2009-2011. Compared with whites, mixed-race individuals had higher odds of CU; Asian Americans and Hispanics had lower odds of CU. There were no significant yearly changes in CUD prevalence in the sample during 2005-2011 (1.58-1.73%). Compared with whites, individuals who were mixed-race, black, and Native American had higher odds of CUD; Asian Americans had lower odds. In aggregate, 15.35% of past-year cannabis users met criteria for a CUD in the 12-month period. Past-year cannabis users who were black, Native American, Hispanic, or Asian American had higher odds of CUD than white users. In each racial/ethnic group, adolescent cannabis users generally showed greater odds of CUD than adult users. Behavioral health indicators (major depressive episode, arrest history, nicotine dependence, and alcohol disorder) were associated with CU and CUD. In conclusion, CUD disproportionately affects nonwhite groups and youth.

**High Rates of Unprotected Anal Intercourse with Regular and Casual Partners and Associated Risk Factors In a Sample of Ethnic Malay Men Who Have Sex With Men (MSM) in Penang, Malaysia** Lim SH, Bazazi AR, Sim C, Choo M, Altice FL, Kamarulzaman A. Sex Transm Infect. 2013; 89(8): 642-649.

The aim of this study was to assess the prevalence of unprotected anal intercourse (UAI) and its correlates among ethnic Malay men who have sex with men (MSM). In 2010, a convenience sample of 350 MSM in Penang were recruited to participate in an anonymous, computerized survey with rapid HIV testing. Participants who were not of Malay ethnicity (n=44) or who did not report sex with another man in the previous 12 months (n=22) were excluded, resulting in 284 participants in the final analysis. Correlates of UAI were examined separately for regular and casual partnerships using bivariate and multivariate logistic regression. Four men (1.9%) tested HIV positive. In the past 12 months, 64.7% of participants had regular sexual partners, 77.1% had casual sexual partners and 41.9% had both. Most participants (83.1%) reported UAI, which was more common in regular partnerships. Over two-thirds of participants had never been tested for HIV. In multivariate analysis, agreement about sexual risk reduction practices was associated with a reduction in UAI with regular partners (adjusted OR (AOR) =0.14, 95% CI 0.05 to 0.40). Reporting difficulty in using condoms was associated with an increase in UAI with casual partners (AOR=9.07, 95% CI 3.35 to 24.5), and any exposure to HIV prevention was associated with a decrease in UAI with casual partners (AOR=0.22, 95% CI 0.09 to 0.54). Despite highly prevalent HIV risk behaviors, HIV seropositivity and prior HIV testing were low. Increasing sexual negotiation skills and access to HIV testing and other prevention services may improve future prevention efforts.

**Association between U.S. State AIDS Drug Assistance Program (ADAP) Features and HIV Antiretroviral Therapy Initiation, 2001-2009** Hanna DB, Buchacz K, Gebo KA, Hessel NA, Horberg MA, Jacobson LP, Kirk GD, Kitahata MM, Korthuis PT, Moore RD, Napravnik S, Patel P, Silverberg MJ, Sterling TR, Willig JH, Collier A, Samji H, Thorne JE, Althoff KN, Martin JN, Rodriguez B, Stuart EA, Gange SJ. PLoS One. 2013; 8(11): e78952.

U.S. state AIDS Drug Assistance Programs (ADAPs) are federally funded to provide antiretroviral therapy (ART) as the payer of last resort to eligible persons with HIV infection. States differ regarding their financial contributions to and ways of implementing these programs and it remains unclear how this interstate variability affects HIV treatment outcomes. The authors analyzed data from HIV-infected individuals who were clinically-eligible for ART between 2001 and 2009 (i.e., a first reported CD4+ <350 cells/uL or AIDS-defining illness) from 14 U.S. cohorts of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Using propensity score matching and Cox regression, the authors assessed ART initiation (within 6 months following eligibility) and virologic suppression (within 1 year) based on differences in two state ADAP features: the amount of state funding in annual ADAP budgets and the implementation of waiting lists. The authors performed an a priori subgroup analysis in persons with a history of injection drug use (IDU). Among 8,874 persons, 56% initiated ART within six months following eligibility. Persons living in states with no additional state contribution to the ADAP budget initiated ART on a less timely basis (hazard ratio [HR] 0.73, 95% CI 0.60-0.88). Living in a state with an ADAP waiting list was not associated with less timely initiation (HR 1.12, 95% CI 0.87-1.45). Neither additional state contributions nor waiting lists were significantly associated with virologic suppression. Persons with an IDU history initiated ART on a less timely basis (HR 0.67, 95% CI 0.47-0.95). The authors found that living in states that did not contribute additionally to the ADAP budget was associated with delayed ART initiation when treatment was clinically indicated. Given the changing healthcare environment, continued assessment of the role of ADAPs and their features that facilitate prompt treatment is needed.

**Risky Sex in Rural America: Longitudinal Changes in a Community-Based Cohort of Methamphetamine and Cocaine Users** Borders TF, Stewart KE, Wright PB, Leukefeld C, Falck RS, Carlson RG, Booth BM.. Am J Addict. 2013; 22(6): 535-542.

This study examined the longitudinal associations between stimulant use and sexual behaviors. Data are from a 3-year community-based study of 710 rural stimulant users. Past 30-day crack cocaine, powder cocaine, and methamphetamine use and sexual behaviors (any sex, inconsistent condom use, and multiple sexual partners) were assessed through in-person interviews every 6 months. GEE analyses revealed that the odds of having sex remained steady over time, with crack cocaine and methamphetamine use positively associated with having sex. The odds of multiple sexual partners declined, but the odds of inconsistent condom use remained steady over time. Crack cocaine use was positively associated with multiple sexual partners, whereas powder cocaine use was negatively associated with inconsistent condom use. Many rural stimulant users could potentially benefit from safe sex educational programs. Such efforts could reduce the incidence of HIV and other STIs in rural America.

**Increased Prospective Health Service Use for Depression among Adults with Childhood Onset Bipolar Disorder** Sala R, Goldstein BI, Wang S, Florez-Salamanca L, Iza M, Blanco C J Pediatr. 2013; 163(5): 1454-7.e1-3.

The aim of this study was to examine the prospective relationship between age of onset of bipolar disorder and the demographic and clinical characteristics, treatment, new onset of psychiatric comorbidity, and psychosocial functioning among adults with bipolar disorder. As part of the National Epidemiologic Survey on Alcohol and Related Conditions, 1600 adults who met lifetime Statistical Manual of Mental Disorders, 4th edition criteria for bipolar disorder-I (n = 1172) and bipolar disorder-II (n = 428) were included. Individuals were evaluated using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV version for Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and data were analyzed from Waves 1 and 2, approximately 3 years apart. Individuals with bipolar disorder were divided into three age at onset groups: childhood (<13 years old, n = 115), adolescence (13-18 years old, n = 396), and adulthood (>19 year old, n = 1017). After adjusting for confounding factors, adults with childhood-onset bipolar disorder were more likely to see a counselor, have been hospitalized, and have received emergency room treatment for depression compared with those with adulthood-onset bipolar disorder. By contrast, there were no differences in the severity of mania or hypomania, new onset of comorbidity, and psychosocial functioning by age of bipolar disorder onset. Childhood-onset bipolar disorder is prospectively associated with seeking treatment for depression, an important proxy for depressive severity. Longitudinal studies are needed in order to determine whether prompt identification, accurate diagnosis, and early intervention can serve to mitigate the burden of childhood onset on the long-term depressive burden of bipolar disorder.

**The Latent Structure and Predictors of Non-Medical Prescription Drug Use and Prescription Drug Use Disorders: A National Study** Blanco C, Rafful C, Wall MM, Jin CJ, Kerridge B, Schwartz RP. Drug Alcohol Depend. 2013; 133(2): 473-479.

Despite growing concerns about non-medical prescription drug use and prescription drug use disorders, whether vulnerability for these conditions is drug-specific or occurs through a shared liability and common risk factors is unknown. Exploratory and confirmatory factor analysis of Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions were used to examine the latent structure of non-medical prescription drug use and prescription drug use disorders. Multiple Indicators Multiple Causes (MIMIC) analysis was used to examine whether the effect of socio-demographic and psychiatric covariates occurred through the latent factor, directly on each drug class or both. A one-factor model described well the structure of both non-medical prescription drug use and

prescription drug use disorders. Younger age, being White, having more intense pain or one of several psychiatric disorders increased the risk of non-medical prescription drug use through the latent factor. The same covariates, except for anxiety disorders also significantly increased the risk of prescription drug use disorders through the latent factor. Older age directly increased the risk of non-medical use of sedatives, and alcohol use disorders decreased the risk of non-medical tranquilizer use. No covariates had direct effects on the risk of any prescription drug use disorders beyond their effect through the latent factor. The risk for non-medical prescription drug use and prescription drug use disorders occurs through a shared liability. Treatment, prevention and policy approaches directed at these drugs as a group maybe more effective than those focused on individual classes of drugs.

**Treatment Considerations for HIV-Infected Individuals with Severe Mental Illness** Blank MB, Himelhoch S, Walkup J, Eisenberg MM. Curr HIV/AIDS Rep. 2013; 10(4): 371-379.

There has been a general recognition of a syndemic that includes HIV/AIDS and severe mental illnesses including schizophrenia, major depression, bipolar disorder, post-traumatic stress disorder, and others. The pathophysiology and direction of effects between severe mental illness and HIV infection is less clear however, and relatively little work has been done on prevention and treatment for people with these complex, co-occurring conditions. Here the authors present the most recent work that has been published on HIV and mental illness. Further, they describe the need for better treatments for "triple diagnosed persons"; those with HIV, mental illness, and substance abuse and dependence. Finally, the authors describe the potential drug-drug interactions between psychotropic medications and anti-retrovirals, and the need for better treatment guidelines in this area. They describe one example of an individually tailored intervention for persons with serious mental illness and HIV (PATH+) that shows that integrated community-based treatments using advanced practice nurses (APNs) as health navigators can be successful in improving health-related quality of life and reducing the burden of disease in these persons.

**The Relationship between Midlife and Late Life Alcohol Consumption, APOE E4 and the Decline in Learning and Memory among Older Adults** Downer B, Zanjani F, Fardo DW. Alcohol. 2014; 49 (1): 17-22.

The aim of the study was to determine whether the trajectory of learning and memory is modified according to an interaction between midlife or late life alcohol consumption status and the presence of one or more APOE e4 alleles. This was a secondary analysis of cognitive, genetic and alcohol consumption data collected from members of the Framingham Heart Study Offspring Cohort. Light and moderate alcohol consumption during late life was associated with greater decline in learning and memory among APOE e4 carriers, whereas light and moderate alcohol consumption was associated with an increase in learning and memory among non-APOE e4 carriers. There was not a significant interaction between midlife alcohol consumption status and APOE e4 on the trajectory of learning and memory. Light to moderate alcohol consumption during late life may protect against a decline in learning and memory for non-APOE e4 allele carriers, but not for older adults who carry one or more APOE e4 alleles.

**Paying the Price: The Pressing Need for Quality, Cost, and Outcomes Data to Improve Correctional Health Care for Older Prisoners** Ahalt C, Trestman RL, Rich JD, Greifinger RB, Williams BA. J Am Geriatr Soc. 2013; 61(11): 2013-2019.

Despite a recent decline in the U.S. prison population, the older prisoner population is growing rapidly. U.S. prisons are constitutionally required to provide health care to prisoners. As the population ages, healthcare costs rise, states are forced to cut spending, and many correctional agencies struggle to meet this legal standard of care. Failure to meet the healthcare needs of older prisoners, who now account



for nearly 10% of the prison population, can cause avoidable suffering in a medically vulnerable population and violation of the constitutional mandate for timely access to an appropriate level of care while incarcerated. Older prisoners who cannot access adequate health care in prison also affect community healthcare systems because more than 95% of prisoners are eventually released many to urban communities where healthcare disparities are common and acute healthcare resources are overused. A lack of uniform quality and cost data has significantly hampered innovations in policy and practice to improve value in correctional health care (achieving desired health outcomes at sustainable costs). With their unique knowledge of complex chronic disease management, experts in geriatrics are positioned to help address the aging crisis in correctional health care. This article delineates the basic health, cost, and outcomes data that geriatricians and gerontologists need to respond to this crisis, identifies gaps in the available data, and anticipates barriers to data collection that, if addressed, could enable clinicians and policy-makers to evaluate and improve the value of geriatric prison health care.

**High Rates of Police Detention among Recently Released HIV-Infected Prisoners in Ukraine: Implications for Health Outcomes** Izenberg JM, Bachiredy C, Soule M, Kiriazova T, Dvoryak S, Altice FL. *Drug Alcohol Depend.* 2013; 133(1): 154-160.

Ukraine's HIV epidemic, primarily affecting people who inject drugs (PWID), is expanding and transitioning despite free opioid substitution therapy (OST) and antiretroviral therapy (ART), two effective ways to reduce HIV transmission. Police detention of PWID not resulting in a formal charge or imprisonment is common, but its prevalence and impact on health are not known. HIV-infected individuals (N=97) released from prison within one year were recruited and surveyed in two HIV-endemic Ukrainian cities about post-release police detention experiences. Data on the frequency of police detention, related adverse events, and impact on OST and ART continuity were collected, and correlates of detention were examined using logistic regression. Detention responses were available for 94 (96.9%) participants, of which 55 (58.5%) reported police detentions (mean=9.4 per person-year). For those detained while prescribed OST (N=28) and ART (N=27), medication interruption was common (67.9% and 70.4%, respectively); 23 of 27 participants prescribed OST (85.2%) were detained en route to/from OST treatment. Significant independent correlates of detention without charges included post-release ART prescription (AOR 4.98,  $p=0.021$ ), current high-risk injection practices (AOR 5.03,  $p=0.011$ ), male gender (AOR 10.88,  $p=0.010$ ), and lower lifetime months of imprisonment (AOR 0.99,  $p=0.031$ ). HIV-infected individuals recently released from prison in Ukraine experience frequent police detentions, resulting in withdrawal symptoms, confiscation of syringes, and interruptions of essential medications, including ART and OST. Structural changes are urgently needed to reduce police detentions in order to control HIV transmission and improve both individual and public health.

**Tuberculosis Screening in a Novel Substance Abuse Treatment Center in Malaysia: Implications for a Comprehensive Approach for Integrated Care** Al-Darraji HAA, Wong KC, Yeow DGE, Fu JJ, Loeliger K, Paiji C, Kamarulzaman A, Altice FL. *J Subst Abuse Treat.* 2014; 46(2): 144-149.

People who use drugs (PWUD) represent a key high risk group for tuberculosis (TB). The prevalence of both latent TB infection (LTBI) and active disease in drug treatment centers in Malaysia is unknown. A cross-sectional convenience survey was conducted to assess the prevalence and correlates of LTBI among attendees at a recently created voluntary drug treatment center using a standardized questionnaire and tuberculin skin testing (TST). Participants (N=196) were mostly men (95%), under 40 (median age=36 years) and reported heroin use immediately before treatment entry (75%). Positive TST prevalence was 86.7%. Nine (4.6%) participants were HIV-infected. Previous arrest/incarcerations (AOR=1.1 for every entry,  $p<0.05$ ) and not being HIV-infected (AOR=6.04,  $p=0.03$ ) were significantly associated with TST positivity. There is an urgent need to establish TB

screening and treatment programs in substance abuse treatment centers and to tailor service delivery to the complex treatment needs of patients with multiple medical and psychiatric co-morbidities.

### **Impact of New Therapeutics for Hepatitis C Virus Infection in Incarcerated Populations**

Spaulding AS, Kim AY, Harzke AJ, Sullivan JC, Linas BP, Brewer A, Dickert J, McGovern BH, Strick LB, Trestman R, Ferguson WJ. *Top Antivir Med.* 2013; 21(1): 27-35.

Inmate populations bear a disproportionate share of the burden of hepatitis C virus (HCV) infection. With more than 90% of prisoners released back to their communities within a few years of sentencing, incarceration can be viewed as an opportunity to provide HCV screening and therapeutic interventions to benefit the individual, reduce the costs of HCV management to the health care system from a societal perspective, and improve overall public health. Although optimal medical management of HCV within prison settings would increase the current cost of correctional health care, it could decrease transmission within the community, reduce overall disease burden, and lower the future societal health care costs associated with end-stage liver disease. Nonetheless, most prison systems treat only a small fraction of infected inmates. Current and emerging therapeutic agents will cure HCV infection in the vast majority of patients. Mathematical modeling also shows that expanded HCV screening and treatment are cost-effective from the societal perspective. In this article, the authors will describe appropriate treatment regimens, propose strategies to lessen the burden of these costly HCV therapies on correctional health care systems, and address the challenges of expanded HCV screening in correctional settings.

### **Secondary Traumatic Stress in Military Primary and Mental Health Care Providers** Kintzle S, Yarvi JS, Bride BE. *Mil Med.* 2013; 178(12): 1310-1315.

The purpose of this study was to explore rates of secondary traumatic stress (STS) in a sample of 70 military primary and mental health care providers. The sample included working professionals within two military hospitals. Participants completed surveys containing a demographic questionnaire and the Secondary Traumatic Stress Scale. Results of data analysis found military participants in the sample to be experiencing relatively low rates of STS. Over half of the sample reported endorsing at least one symptom of STS occurring within the last week, whereas 8% of participants indicated moderate to high symptomatology. The most frequently reported symptoms were feeling emotionally numb and trouble sleeping followed by the intrusive thoughts about clients. The least frequently reported symptom was feeling jumpy. Implications of study findings and recommendations for future research are outlined.

### **Design and Methods of A Double Blind Randomized Placebo-Controlled Trial of Extended-Release Naltrexone for Alcohol Dependent and Hazardous Drinking Prisoners with HIV who Are Transitioning to the Community** Springer SA, Altice FL, Herme M, Di Paola A. *Contemp Clin Trials.* 2013; 37(2): 209-218.

HIV-infected prisoners have a high prevalence of alcohol use disorders and commonly relapse to alcohol soon after release to the community which is linked to high morbidity, poor antiretroviral therapy (ART) adherence and increased sexual risk-taking behaviors. Extended-release naltrexone (XR-NTX) effectively reduces relapse to alcohol in alcohol dependent persons, yet it remains unexamined among criminal justice system (CJS) populations transitioning to the community. A randomized double-blind, placebo-controlled trial of XR-NTX to improve HIV treatment outcomes via reducing relapse to alcohol use after prison release for HIV-infected hazardous drinking and alcohol dependent prisoners is discussed. Acceptability of study participation is high with 86% of those referred who met eligibility criteria and 85% of those who were able to receive injections prior to release accepted injections, yet important implementation issues are identified and addressed during

the study and are discussed in this paper. Medication-assisted therapies for prevention of relapse to alcohol use for CJS populations transitioning to the community, especially for HIV-infected patients, are urgently needed in order to reduce alcohol relapse after release and improve HIV treatment outcomes and contribute to improved individual and public health.

**Probability and Predictors of First Treatment Contact for Anxiety Disorders in the United States: Analysis of Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)** Iza M, Olfson M, Vermes D, Hoffer M, Wang S, Blanco C. J Clin Psychiatry. 2013; 74(11): 1093-1100.

Despite the high prevalence of anxiety disorders and the demonstrated efficacy of their treatment, most individuals with anxiety disorders never utilize mental health services. To identify predictors of treatment-seeking for DSM-IV anxiety disorders from a range of socio-demographic factors and comorbid mental disorders. Survival analysis with time-varying covariates was performed using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Face-to-face interviews conducted in the United States. 34,653 respondents, aged 18 years and older, from the 2004-2005 Wave 2 NESARC. The cumulative probability of treatment-seeking (assessed by the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV version, Wave 2 version) across the anxiety disorders in 1 year, 10 years, and lifetime and the median delay to the first treatment contact. Most individuals with panic disorder sought treatment within the same year of disorder onset, whereas the median delays to first treatment contact for generalized anxiety disorder, specific phobia, and social anxiety disorder were 1 year, 13 years, and 16 years, respectively. Several personality disorders and earlier age at anxiety disorder onset decreased the probability of treatment contact. By contrast, younger cohort membership, a recent change in marital status, treatment for a psychiatric disorder other than substance use disorder, and comorbid anxiety disorders increased the lifetime probability of treatment contact. Treatment-seeking rates for most anxiety disorders are low, are associated with long delays, and sometimes are hindered by co-occurrence of other psychopathology. These patterns highlight the complex interplay of personal characteristics, individual psychopathology, and social variables in the treatment-seeking process.

**Latent Structure of Social Fears and Social Anxiety Disorders** Iza M, Wall MM, Heimberg RG, Rodebaugh TL, Schneier FR, Liu S-M, Blanco C. Psychol Med. 2014; 44(2): 361-370.

Despite its high prevalence and associated levels of impairment, the latent structure of social anxiety disorder (SAD) is not well understood, with published studies reporting inconsistent results. Furthermore, it is unknown whether the latent structure of social fears in individuals with and without SAD is the same. Exploratory factor analysis (EFA) and confirmatory factor analysis followed by multiple indicators multiple causes (MIMIC) analysis were conducted on 13 commonly feared social situations assessed in a nationally representative sample including individuals with SAD and those with social fears but who did not meet DSM-IV criteria for SAD. An EFA conducted in the full sample, including individuals with no social fears (88% of the sample), yielded only one factor. When the sample was restricted to those with at least one social fear, the EFA yielded three factors, in both the subsample with at least one social fear but no SAD and the subsample with SAD. The three factors represented feared situations related to public performance, close scrutiny and social interaction. The MIMIC analyses further indicated that the three-factor structure was able to explain differences in prevalence of social fears across a broad range of sociodemographic covariates. Among individuals with at least one social fear and those with DSM-IV SAD the latent structure of social fears appears to be best described by three factors, although this may partially depend on how the sample is specified. These results may help reconcile the findings of different numbers of factors identified in previous studies.

**Remission from Substance Dependence: Differences between Individuals in A General Population Longitudinal Survey Who Do and Do Not Seek Help** Grella CE, Stein JA. Drug Alcohol Depend. 2013; 133(1): 146-153.

Only a minority of individuals who have substance use disorders receives treatment, and those who do typically have more severe disorders. The current study examines the relationship of help-seeking with remission from alcohol and/or drug dependence and other outcomes. Data from the Wave 1 (2001-2002) and Wave 2 (2004-2005) National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) were used to examine remission at Wave 2 among respondents who had past-year substance dependence disorders at Wave 1 (N=1262). Multi-group structural equation modeling was used to compare individuals with (n=356) and without (n=906) prior help-seeking at Wave 1 on subsequent help-seeking and other factors that influence outcomes. Baseline help-seekers sought help at higher levels over the follow-up period (31% vs. 8%) and had lower rates of remission (50% vs. 68%), as compared with those without prior help-seeking, respectively. Among baseline help-seekers, there were stronger relationships between baseline stress and mental disorders and having sought help since baseline; age and past-year level of stress at follow-up; level of stress and health status at follow-up; and social support and mental disorders at follow-up. Among baseline non-help-seekers, there were stronger relationships between being female and past-year stress at follow-up, and between having sought help since baseline and physical health status at follow-up. Findings extend our understanding of the factors associated with recovery from substance dependence, including "natural recovery", use of services outside of addiction treatment, and gender differences in help-seeking and remission.

**Meeting Health and Psychological Needs of Women in Drug Treatment Court** Morse DS, Cerulli C, Bedell P, Wilson JL, Thomas K, Mitta M, Lamberti JS, Williams G, Silverstein J, Mukherjee A, Walck D, Chin N. J Subst Abuse Treat. 2014; 46(2): 150-157.

The authors explored healthcare-related experiences of women drug court participants through combining context from the socio-ecological model with motivation needs for health behavior as indicated by self-determination theory. Five focus groups with 8 women drug court participants, 8 court staff, and 9 community service providers were examined using qualitative framework analysis. Themes emerged across the socio-ecological model and were cross-mapped with self-determination theory-defined motivation needs for autonomy, relatedness, and competence. Socio-ecological levels contained experiences either supporting or eroding women's motivation needs: 1) intrapersonal challenges participants termed an "evil cycle" of relapse, recidivism, trauma, and life challenges; 2) interpersonal context of parenting and stigma involving features of this "evil cycle"; 3) institutions with logistical barriers to legal and medical assistance; 4) community resources inadequate to support living and employment needs. Self-determination theory helps explain motivation required to address the women's healthcare needs and multiple demands at all levels of the socio-ecological model.

**Dynamic Social Networks in Recovery Homes** Jason LA, Light JM, Stevens EB, Beers K. Am J Community Psychol 2013 Nov 12 [e-pub ahead of print].

Acute treatment aftercare in the form of sober living environments-i.e., recovery houses-provide an inexpensive and effective medium-term treatment alternative for many with substance use disorders. Limited evidence suggests that house-situated social relationships and associated social support are critical determinants of how successful these residential experiences are for their members, but little is known about the mechanisms underlying these relationships. This study explored the feasibility of using dynamic social network modeling to understand house-situated longitudinal associations among individual Alcoholics Anonymous related recovery behaviors, length of residence, dyadic interpersonal trust, and dyadic confidant relationship formation processes. Trust and confidant relationships were measured 3 months apart in U.S. urban-area recovery houses, all of which were part of a network of

substance use recovery homes. A stochastic actor-based model was successfully estimated from this data set. Results suggest that confidant relationships are predicted by trust, while trust is affected by recovery behaviors and length of residence. Conceptualizing recovery houses as a set of independent, evolving social networks that can be modeled jointly appears to be a promising direction for research.

### **Predictive Validity of Dynamic Factors: Assessing Violence Risk in Forensic Psychiatric**

**Inpatients** Wilson CM, Desmarais, SL, Nicholls TL, Hart SD, Brink J. *Law Hum Behav.* 2013; 37(6): 377-388.

There is general consensus that dynamic factors ought to be considered in the assessment of violence risk, but little direct evidence exists to demonstrate that within-individual fluctuations in putative dynamic factors are associated with changes in risk. The authors examined these issues in a sample of 30 male forensic psychiatric inpatients using a pseudoprospective design. Static and dynamic factors were coded on the basis of chart review using 2 structured measures of violence risk: Version 2 of the Historical-Clinical-Risk Management-20 (HCR-20; C.D. Webster, K.S. Douglas, D. Eaves, & S.D. Hart, 1997, HCR-20: Assessing risk for violence, Version 2, Vancouver, BC, Canada: Mental Health, Law, and Policy Institute, Simon Fraser University) and the Short-Term Assessment of Risk and Treatability (START; C.D. Webster, M.L. Martin, J. Brink, T.L. Nicholls, & S.L. Desmarais, 2009, Short-Term Assessment of Risk and Treatability [START], Version 1.1, Coquitlam, BC, Canada: British Columbia Mental Health and Addiction Services). HCR-20 and START assessments were repeated every 3 months for a period of 1 year. Institutional violence in the 3 months following each assessment was coded using a modified version of the Overt Aggression Scale (S.C. Yudofsky, J.M. Silver, W. Jackson, J. Endicott, & D.W. Williams, 1986, The Overt Aggression Scale for the objective rating of verbal and physical aggression, *The American Journal of Psychiatry*, Vol. 143, pp. 35-39). Dynamic risk and strength factors showed predictive validity for institutional aggression. Results of event history analyses demonstrated that changes in dynamic risk factors significantly predicted institutional violence, even after controlling for static risk factors. This is one of the first studies to provide clear and direct support for the utility of dynamic factors in the assessment of violence risk.

### **RCT of A Promising Vocational/Employment Program for High-Risk Juvenile Offenders**

Schaeffer CM, Henggeler SW, Ford JD, Mann M, Chang R, Chapman JE. *J Subst Abuse Treat.* 2014; 46(2): 134-143.

Juvenile offenders with substance use problems are at high risk for deleterious long-term outcomes. This study evaluated the capacity of a promising vocational and employment training program in the building sector (i.e., Community Restitution Apprenticeship-Focused Training, CRAFT) to mitigate such outcomes through enhanced employment and education. Participants were 97 high-risk juvenile offenders (mean age=15.8 years) randomized to CRAFT versus education as usual (EAU) intervention conditions. Multi-method procedures measured employment, education, substance use, mental health, and criminal outcomes through a 30-month post-baseline follow-up. CRAFT was significantly more effective than EAU at increasing rates of youth employment and GED attendance. Intervention effects were not observed, however, for months employed, hours worked, or hourly wage. Measures of youth substance use, mental health symptoms, and criminal activity showed no favorable or iatrogenic effects. The potential of CRAFT was modestly supported, and suggestions were made for future research.

**Physicians Criticizing Physicians to Patients** McDaniel SH, Morse DS, Reis S, Edwardsen EA, Gurnsey MG, Taupin A, Griggs JJ, Shields CG. *J Gen Intern Med.* 2013; 28(11): 1405-1409.

Teamwork is critical to providing excellent healthcare, and effective communication is essential for teamwork. Physicians often discuss patient referrals from other physicians, including referrals from

outside their primary institution. Sharing conflicting information or negative judgments of other physicians to patients may be unprofessional. Poor teamwork within healthcare systems has been associated with patient mortality and lower staff well-being. This analysis explored how physicians talk to patients with advanced cancer about care rendered by other physicians. Standardized patients (SPs) portraying advanced lung cancer attended covertly recorded visits with consenting oncologists and family physicians. Twenty community-based oncologists and 19 family physicians had encounters with SPs. Physician comments about care by other physicians were extracted from transcriptions and analyzed qualitatively. These comments were categorized as Supportive or Critical. The authors also examined whether there were differences between physicians who provide supportive comments and those who provided critical comments. Fourteen of the 34 encounters (41 %) included in this analysis contained a total of 42 comments about the patient's previous care. Twelve of 42 comments (29 %) were coded as Supportive, twenty-eight (67 %) as Critical, and two (4 %) as Neutral. Supportive comments attributed positive qualities to another physician or their care. Critical comments included one specialty criticizing another and general lack of trust in physicians. This study described comments by physicians criticizing other physicians to patients. This behavior may affect patient satisfaction and quality of care. Healthcare system policies and training should discourage this behavior.

**Psychometric Properties of the Adjective Rating Scale for Withdrawal across Treatment Groups, Gender, and Over Time**

Barbosa-Leiker C, McPherson S, Mamey MR, Burns GL, Roll J. J Subst Abuse Treat. 2014; 46(2): 251-256.

The Adjective Rating Scale for Withdrawal (ARSW) is commonly used to assess opiate withdrawal in clinical practice and research. The aims of this study were to examine the factor structure of the ARSW, test measurement invariance across gender and treatment groups, and assess longitudinal measurement invariance across the clinical trial. Secondary data analysis of the National Drug Abuse Treatment Clinical Trials Network 000-3, a randomized clinical trial comparing two tapering strategies, was performed. The ARSW was analyzed at baseline, end of taper and 1-month follow-up (N=515 opioid-dependent individuals). A 1-factor model of the ARSW fit the data and demonstrated acceptable reliability. Measurement invariance was supported across gender and taper groups. Longitudinal measurement invariance was not found across the course of the trial, with baseline assessment contributing to the lack of invariance. If change over time is of interest, change from post-treatment through follow-up may offer the most valid comparison.

**Does Age at First Treatment Episode Make A Difference in Outcomes Over 11 Years?**

Chi FW, Weisner C, Grella CE, Hser Y-I, Moore C, Mertens J. J Subst Abuse Treat. 2014 Apr; 46(4): 482-490. This study examines the associations between age at first substance use treatment entry and trajectory of outcomes over 11 years. The authors found significant differences in individual and treatment characteristics between adult intakes first treated during young adulthood (25years or younger) and those first treated at an older age. Compared to their first treated older age counterparts matched on demographics and dependence type, those who entered first treatment during young adulthood had on average an earlier onset for substance use but a shorter duration between first substance use and first treatment entry; they also had worse alcohol and other drug outcomes 11 years post treatment entry. While subsequent substance use treatment and 12-step meeting attendance are important for both age groups in maintaining positive outcomes, relationships varied by age group. Findings underline the importance of different continuing care management strategies for those entering first treatment at different developmental stages.

**Alcohol Stigma and Persistence of Alcohol and Other Psychiatric Disorders: A Modified Labeling Theory Approach**

Glass JE, Mowbray OP, Link BG, Kristjansson SD, Bucholz KK. Drug Alcohol Depend. 2013; 133(2): 685-692.

The authors sought to apply modified labeling theory in a cross-sectional study of alcohol use disorder (AUD) to investigate the mechanisms through which perceived alcohol stigma (PAS) may lead to the persistence of AUD and risk of psychiatric disorder. They conducted structural equation modeling (SEM) including moderated mediation analyses of two waves (W1 and W2) of data from the National Epidemiologic Survey on Alcohol and Related Conditions. They analyzed validated measures of PAS, perceived social support, social network involvement, and psychiatric disorders among (n=3608) adults with two or more DSM-5 AUD symptoms in the first two of the three years between the W1 and W2 survey. Cross-sectional analyses were conducted owing to the assessment of PAS only at W2. Per mediation analyses, lower levels of perceived social support explained the association of PAS with past-year AUD and past-year internalizing psychiatric disorder at W2. The size of the mediated relationship was significantly larger for those classified as labeled (i.e., alcoholic) per their prior alcohol treatment or perceived need (n=938) as compared to unlabeled (n=2634), confirming a hypothesis of moderated mediation. Unexpectedly, mediation was also present for unlabeled individuals. Lower levels of social support may be an important intermediate outcome of alcohol stigma. Longitudinal data are needed to establish the temporal precedence of PAS and its hypothesized intermediate and distal outcomes. Research is needed to evaluate direct measures of labeling that could replace proxy measures (e.g., prior treatment status) commonly employed in studies of the stigma of psychiatric disorders.

**Comparing Barriers to Mental Health Treatment and Substance Use Disorder Treatment among Individuals with Comorbid Major Depression and Substance Use Disorders**

Mojtabai R, Chen L-Y, Kaufmann CN, Crum RM. J Subst Abuse Treat. 2014; 46(2): 268-273.

Barriers to both mental health and substance use disorder treatments have rarely been examined among individuals with comorbid mental health and substance use disorders. In a sample of 393 adults with 12-month major depressive episodes and substance use disorders, the authors compared perceived barriers to these two types of treatments. Data were drawn from the 2005-2011 U.S. National Surveys on Drug Use and Health. Overall, the same individuals experienced different barriers to mental health treatment versus substance use disorder treatment. Concerns about negative views of the community, effects on job, and inconvenience of services were more commonly reported as reasons for not receiving substance use disorder treatment. Not affording the cost of care was the most common barrier to both types of treatments, but more commonly reported as a barrier to mental health treatment. Improved financial access through the Affordable Care Act and parity legislation and integration of mental health and substance use disorder services may help to reduce treatment barriers among individuals with comorbid mental health and substance disorders.

**The Roles of Spirituality in the Relationship between Traumatic Life Events, Mental Health, and Drug Use Among African American Women from One Southern State**

Staton-Tindall M, Duvall J, Stevens-Watkins D, Oser CB. Subst Use Misuse. 2013; 48(12): 1246-1257.

This study examines the role of spirituality as a moderator of the relationship between traumatic life experiences, mental health, and drug use in a sample of African American women. It was hypothesized that there would be an inverse relationship overall between spirituality and mental health and drug use among this sample of African American women. Secondly, was expected that spirituality would moderate the relationship between traumatic life events and mental health and drug use. African American women (n = 206) were recruited from the community and from probation officers in three

urban areas of a southern state, and face-to-face interviews were completed. Findings indicated that there was a main effect for spirituality (as measured by existential well-being on the Spiritual Well-Being Scale) and traumatic life events, mental health, and alcohol use. In addition, spirituality was a significant moderator of the relationship between traumatic life events and cocaine use. Discussion and implications for African American women are included.

**Reliability of Therapist Self-Report on Treatment Targets and Focus in Family-Based**

**Intervention** Hogue A, Dauber S, Henderson CE, Liddle HA. Adm Policy Ment Health. 2013 Sept 26 [e-pub ahead of print].

Reliable therapist-report methods appear to be an essential component of quality assurance procedures to support adoption of evidence-based practices in usual care, but studies have found weak correspondence between therapist and observer ratings of treatment techniques. This study examined therapist reliability and accuracy in rating intervention target (i.e., session participants) and focus (i.e., session content) in a manual-guided, family-based preventive intervention implemented with 50 inner-city adolescents at risk for substance use. A total of 106 sessions selected from three phases of treatment were rated via post-session self-report by the participating therapist and also via videotape by nonparticipant coders. Both groups estimated the amount of session time devoted to model-prescribed treatment targets (adolescent, parent, conjoint) and foci (family, school, peer, prosocial, drugs). Therapists demonstrated excellent reliability with coders for treatment targets and moderate to high reliability for treatment foci across the sample and within each phase. Also, therapists did not consistently overestimate their degree of activity with targets or foci. Implications of study findings for fidelity assessment in routine settings are discussed.



## **CTN-RELATED RESEARCH**

### **Internet-delivered Treatment for Substance Abuse: A Multi-site Randomized Controlled Clinical Trial**

Campbell AN, Nunes EV, Matthews AG, Stitzer M, Miele GM, Polsky D, Turrigiano E, Walters S, McClure EA, Kyle TL, Wahle A, Van Veldhuisen P, Goldman B, Babcock D, Stabile PQ, Winhusen T, Ghitza UE. Am J Psychiatry. 2014 Apr 4. [Epub ahead of print].

Computer-delivered interventions have the potential to improve access to quality addiction treatment care. The objective of this study was to evaluate the effectiveness of the Therapeutic Education System (TES), an Internet-delivered behavioral intervention that includes motivational incentives, as a clinician-extender in the treatment of substance use disorders. Adult men and women (N=507) entering 10 outpatient addiction treatment programs were randomly assigned to receive 12 weeks of either treatment as usual (N=252) or treatment as usual plus TES, with the intervention substituting for about 2 hours of standard care per week (N=255). TES consists of 62 computerized interactive modules covering skills for achieving and maintaining abstinence, plus prize-based motivational incentives contingent on abstinence and treatment adherence. Treatment as usual consisted of individual and group counseling at the participating programs. The primary outcome measures were abstinence from drugs and heavy drinking (measured by twice-weekly urine drug screens and self-report) and time to dropout from treatment. Compared with patients in the treatment-as-usual group, those in the TES group had a lower dropout rate (hazard ratio=0.72, 95% CI=0.57, 0.92) and a greater abstinence rate (odds ratio=1.62, 95% CI=1.12, 2.35). This effect was more pronounced among patients who had a positive urine drug or breath alcohol screen at study entry (N=228) (odds ratio=2.18, 95% CI=1.30, 3.68). The authors conclude that internet-delivered interventions such as TES have the potential to expand access and improve addiction treatment outcomes. Additional research is needed to assess effectiveness in non-specialty clinical settings and to differentiate the effects of the community reinforcement approach and contingency management components of TES.

### **Changes In Sleep Disruption In the Treatment Of Co-Occurring Posttraumatic Stress Disorder and Substance Use Disorders**

McHugh RK, Hu MC, Campbell AN, Hilario EY, Weiss RD, Hien DA. J Trauma Stress. 2014 Feb; 27(1): 82-89.

Sleep disruption appears not only to reflect a symptom of posttraumatic stress disorder (PTSD), but also a unique vulnerability for its development and maintenance. Studies examining the impact of psychosocial treatments for PTSD on sleep symptoms are few and no studies to date of which the authors are aware have examined this question in samples with co-occurring substance use disorders. The current study is a secondary analysis of a large clinical trial comparing 2 psychological treatments for co-occurring PTSD and substance use disorders. Women (N = 353) completed measures of PTSD at baseline, end of treatment, and 3-, 6-, and 12-month follow-ups. Results indicated that the prevalence of insomnia, but not nightmares, decreased during treatment, and that 63.8% of participants reported at least 1 clinical-level sleep symptom at the end of treatment. Improvement in sleep symptoms during treatment was associated with better overall PTSD outcomes over time,  $\chi^2(1) = 33.81, p < .001$ . These results extend the existing literature to suggest that residual sleep disruption following PTSD treatment is common in women with co-occurring PTSD and substance use disorders. Research on the benefits of adding sleep-specific intervention for those with residual sleep disruption in this population may be a promising future direction.

**Methadone Maintenance For HIV Positive and HIV Negative Patients In Kyiv: Acceptability and Treatment Response**

Dvoriak S, Karachevsky A, Chhatre S, Booth R, Metzger D, Schumacher J, Chychula N, Pecoraro A, Woody G. Drug Alcohol Depend. 2014 Apr 1; 137: 62-67.

With up to 40% of opioid injectors infected with HIV, Ukraine has one of the most concentrated HIV epidemics in the world, mainly due to unsterile injection practices and a historical absence of effective prevention services. Harm reduction programs, including syringe exchange and a small buprenorphine treatment program, were introduced in 2004 and methadone maintenance was allowed in 2007. Despite an initial expansion, by 2009, only 3221 injectors were receiving methadone treatment. A growing body of research on methadone maintenance has found high retention rates with reduction in opioid use and HIV risk behaviors. The authors report on the acceptability and initial outcome of methadone treatment as a function of HIV status, an issue that has not yet been reported for injectors in Ukraine. This was a longitudinal observational study of a 12-week course of methadone treatment in 25 HIV+ and 25 HIV- opioid addicted individuals recruited from a harm reduction program and the city AIDS Center. Drug use and HIV risk were assessed at baseline and weeks 4, 8, 12 and 20; all patients were offered continued methadone maintenance in the Kyiv city program at the end of 12 weeks. Fifty-four individuals were asked if they were interested in the study and 50, demographically similar to other samples of opioid addicted Ukrainians, agreed to participate. Two died of non-study related causes; the other 48 completed assessments at weeks 4, 8 and 12, and 47 completed followups at week 20. Significant reductions were seen in use of heroin ( $p<0.0001$ ), other opiates/analgesics ( $p<0.0001$ ), and HIV risk behaviors (drug, sex, total; all  $p<0.0001$ ). All 48 patients chose to continue methadone after the 12-weeks of study medication ended. Unlike most opioid treatment studies, sexual risk was somewhat higher than injecting risk at study intake. The authors conclude that methadone maintenance was well accepted by HIV+ and HIV- opioid dependent individuals and has the potential for significant public health impact if made more widely available with sustained access and support.

## **WOMEN AND SEX/GENDER DIFFERENCES-RELATED RESEARCH**

### **Women and Smoking: The Effect of Gender on the Epidemiology, Health Effects and Cessation of Smoking**

Allen AM, Oncken C, Hatsukami D. 2014. Current Addiction Reports; 1: 53-60.

Smoking is still the leading cause of premature morbidity and mortality. This paper examines new research on gender differences and the epidemiology of smoking, smoking-related morbidity and mortality, and factors that affect smoking cessation. The rate of decline in the prevalence of smoking has been slowing, especially among adolescent girls. New research suggests that, compared with men, women may be more susceptible to smoking-related morbidity and mortality. Gender-related barriers to smoking cessation include weight gain, sex hormones, and mood. Furthermore, the sensory aspects of smoking may have more of an effect on smoking treatment for women than for men. The authors discuss new studies that examine smoking-cessation interventions that may be particularly beneficial for women, including exercise (as an adjunct intervention), very low nicotine content cigarettes, and a variety of pharmacotherapy. Further research is needed to identify and target the gender-specific needs of smokers.

### **Subjective, Physiological, and Cognitive Responses to Intravenous Nicotine: Effects of Sex and Menstrual Cycle Phase**

DeVito EE, Herman, AI, Waters AJ, Valentine GW, Sofuoglu M.

Neuropsychopharmacology. 2014 Jan: 1-10.

Nicotine dependence is a serious public health concern. Optimal treatment of nicotine dependence will require greater understanding of the mechanisms that contribute to the maintenance of smoking behaviors. A growing literature indicates sex and menstrual phase differences in responses to nicotine. The aim of this study was to assess sex and menstrual phase influences on a broad range of measures of nicotine response including subjective drug effects, cognition, physiological responses, and symptoms of withdrawal, craving, and affect. Using a well-established intravenous nicotine paradigm and biochemical confirmation of overnight abstinence and menstrual cycle phase, analyses were performed to compare sex (age 18–50 years; 115 male and 45 female) and menstrual cycle phase (29 follicular and 16 luteal) effects. Females had diminished subjective drug effects of, but greater physiological responses to, nicotine administration. Luteal-phase females showed diminished subjective drug effects and better cognition relative to follicular-phase women. These findings offer candidate mechanisms through which the luteal phase, wherein progesterone is dominant relative to estradiol, may be protective against vulnerability to smoking.

### **Pharmacogenetics of Nicotine Addiction: Role of Dopamine**

Herman AL, DeVito EE, Jensen KP, Sofuoglu M. Pharmacogenomics. 2014 Feb; 15(2): 221-234.

The neurotransmitter dopamine (DA) plays a central role in addictive disorders, including nicotine addiction. Specific DA-related gene variants have been studied to identify responsiveness to treatment for nicotine addiction. Genetic variants in DRD2, DRD4, ANKK1, DAT1, COMT and DBH genes show some promise in informing personalized prescribing of smoking cessation pharmacotherapies. However, many trials studying these variants had small samples, used retrospective design or were composed of mainly self-identified Caucasian individuals. Furthermore, many of these studies lacked a comprehensive measurement of nicotine metabolism rate, did not assess the roles of sex or the menstrual cycle, and did not investigate the role of rare variants and/or epigenetic factors. Future work should be conducted addressing these limitations to more effectively utilize DA genetic information to unlock the potential of smoking cessation pharmacogenetics.

**Understanding Disparities in Subpopulations of Women Who Smoke** Smith MV, Ramsey C, Mazure CM. Current Addiction Reports. 2014 Mar; 1(1): 69-74.

Tobacco use is the leading known cause of preventable death and disease among women. In this paper the authors use fundamental concepts and definitions from the general health-disparities literature to examine smoking behavior among subpopulations of women. They focus on three factors associated with disparities in smoking behavior among subgroups of women-race and/or ethnicity, educational status, and acculturation. They suggest that research on smoking behavior among subpopulations of women is beginning to reveal not only different smoking behavior but disparities among women in different subpopulations. They conclude that subpopulation-based understanding of gender differences and disparities in smoking is critical to improvement of research design, intervention objectives, and public health policy on smoking in women.

**The Effects of Prenatal Cocaine, Post-weaning Housing and Sex on Conditioned Place Preference in Adolescent Rats** Dow-Edwards D, Iijima M, Stephenson S, Jackson A, Weedon J.

Psychopharmacology (Berl). 2014 Jan 17. [Epub ahead of print].

Gestational exposure to cocaine now affects several million people including adolescents and young adults. Whether prenatal drug exposures alter an individual's tendency to take and/or abuse drugs is still a matter of debate. This study sought to answer the question "Does prenatal exposure to cocaine, in a dose-response fashion, alter the rewarding effects of cocaine using a conditioned place preference (CPP) procedure during adolescence in the rat?" Further, the authors wanted to assess the possible sex differences and the role of being raised in an enriched versus impoverished environment. Virgin female Sprague-Dawley rats were dosed daily with cocaine at 30 mg/kg (C30), 60 mg/kg (C60), or vehicle intragastrically prior to mating and throughout gestation. Pups were culled, fostered and, on postnatal day (PND) 23, placed into isolation cages or enriched cages with three same-sex littermates and stimulus objects. On PND43-47, CPP was determined across a range of cocaine doses. C30 exposure increased sensitivity to the rewarding effects of cocaine in adolescent males, and being raised in an enriched environment further enhanced this effect. Rats exposed to C60 resembled the controls in cocaine CPP. Overall, females were modestly affected by prenatal cocaine and enrichment. These data support the unique sensitivity of males to the effects of gestational cocaine, that moderate prenatal cocaine doses produce greater effects on developing reward circuits than high doses and that housing condition interacts with prenatal treatment and sex such that enrichment increases cocaine CPP mostly in adolescent males prenatally exposed to moderate cocaine doses.

**A Randomized, Placebo-Controlled, Double-Blind Trial of Sertraline for Postpartum Depression**

Hantsoo L, Ward-O'Brien D, Czarkowski KA, Gueorguieva R, Price LH, Epperson CN.

Psychopharmacology (Berl). 2014 Mar; 231(5): 939-948. doi: 10.1007/s00213-013-3316-1. Epub 2013 Oct 31.

Postpartum depression (PMD) occurs in roughly 10 % of postpartum women and negatively impacts the mother and her offspring, but there are few placebo-controlled studies of antidepressant treatment in this population. The objective of this study is to compare the selective serotonin reuptake inhibitor (SSRI) sertraline to placebo for treating PMD. This was a single-center, 6-week, randomized double-blind placebo-controlled trial of sertraline with a 1-week placebo lead-in. The participants (n=38) were women with depression onset within 3 months of delivery; a subset (n=27) met strict DSM-IV criteria for PMD (onset within 4 weeks of delivery). The participants were prescribed sertraline 50 mg or placebo daily to a maximum of 200 mg/day. Primary outcome variables were the Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impressions (CGI) scores, which were used to determine the rates of response and remission. Sertraline produced a significantly greater response rate (59 %) than placebo (26 %) and a more than twofold increased remission rate (53 % vs. 21 %). Mixed models

did not reveal significant group by time effects, although in the subset of women who met the DSM-IV criteria, there was a statistically significant group by time effect for the HAM-D, Hamilton Anxiety Rating Scale (HAM-A), and CGI. The authors conclude that women with PMD are more likely to have a remission of their depression with sertraline treatment, a finding that is more pronounced in women who have onset of depression within 4 weeks of childbirth. These data support the continued use of 4 weeks for the DSM-5 postpartum onset specifier for major depressive disorder.

**Elevated Risk of Adverse Obstetric Outcomes in Pregnant Women with Depression** Kim DR, Sockol LE, Sammel MD, Kelly C, Moseley M, Epperson CN. Arch Womens Ment Health. 2013 Dec;16(6): 475-482. doi: 10.1007/s00737-013-0371-x. Epub 2013 Aug 10.

In this study, the authors evaluated the association between prenatal depression symptoms adverse birth outcomes in African-American women. They conducted a retrospective cohort study of 261 pregnant African-American women who were screened with the Edinburgh Postnatal Depression Scale (EPDS) at their initial prenatal visit. Medical records were reviewed to assess pregnancy and neonatal outcomes, specifically preeclampsia, preterm birth, intrauterine growth retardation, and low birth weight. Using multivariable logistic regression models, an EPDS score  $\geq 10$  was associated with increased risk for preeclampsia, preterm birth, and low birth weight. An EPDS score  $\geq 10$  was associated with increased risk for intrauterine growth retardation, but after controlling for behavioral risk factors, this association was no longer significant. Patients who screen positive for depression symptoms during pregnancy are at increased risk for multiple adverse birth outcomes. In a positive, patient-rated depression screening at the initial obstetrics visit, depression is associated with increased risk for multiple adverse birth outcomes. Given the retrospective study design and small sample size, these findings should be confirmed in a prospective cohort study.

## **INTRAMURAL RESEARCH**

### **Molecular Targets and Medications Discovery Research Branch**

#### **Medicinal Chemistry Section**

**Single Molecule Analysis Reveals Coexistence of Stable Serotonin Transporter Monomers and Oligomers in the Live Cell Plasma Membrane** Anderluh A, Klotzsch E, Reismann AWA, Brameshuber M, Kudlacek O, Newman AH, Sitte HH, Schutz GJ. J Biol Chem 2014; 289(7): 4387-4394.

The human serotonin transporter (hSERT) is responsible for the termination of synaptic serotonergic signaling. While there is solid evidence that SERT forms oligomeric complexes, the exact stoichiometry of the complexes and the fractions of different co-existing oligomeric states still remain enigmatic. Here the authors used single molecule fluorescence microscopy to obtain the oligomerization state of the SERT via brightness analysis of single diffraction limited fluorescent spots. Heterologously expressed SERT was labeled either with the fluorescent inhibitor JHC 1-64, or via fusion to mGFP. They found a variety of oligomerization states of membrane-associated transporters, revealing molecular associations larger than dimers and demonstrating the coexistence of different degrees of oligomerization in a single cell; the data is in agreement with a linear aggregation model. Furthermore, oligomerization was found to be independent of SERT surface density and oligomers remained stable over several minutes in the live cell plasma membrane. Together, the results indicate kinetic trapping of preformed SERT oligomers at the plasma membrane.

**Elucidation of Structural Elements for Selectivity across Monoamine Transporters: Novel 2-[(diphenylmethyl)sulfinyl]acetamide (Modafinil) Analogues** Okunola-Bakara O, Cao J, Kopajtic T, Katz JL, Loland CJ, Shi L, Newman AH. J Med Chem 2014; 57: 1000-1013.

2-[(Diphenylmethyl)sulfinyl]acetamide (modafinil, ( $\pm$ )-1) is a unique dopamine uptake inhibitor that binds the dopamine transporter (DAT) differently from cocaine and may have potential for the treatment of psychostimulant abuse. To further investigate structural requirements for this divergent binding mode, novel thio- and sulfinylacetamide and ethanamine analogues of ( $\pm$ )-1 were synthesized wherein 1) the diphenyl rings were substituted with methyl, trifluoromethyl and halogen substituents and 2) substituents were added to the terminal amide/amine nitrogen. Halogen substitution of the diphenyl rings of ( $\pm$ )-1 gave several amide analogues with improved binding affinity for DAT and robust selectivity over the serotonin transporter (SERT), whereas affinity improved at SERT over DAT for the para-halo-substituted amine analogues. Molecular docking studies, using a subset of analogues with DAT and SERT homology models, and functional data obtained with DAT (A480T) and SERT (T497A) mutants defined a role for TM10 in the substrate/inhibitor S1 binding sites of DAT and SERT.

**Beyond Small Molecule SAR – Using the Dopamine D3 Receptor Crystal Structure to Guide Drug Design** Keck TM, Burzynski C, Shi L, Newman AH Advances in Pharmacology, 2014; 69: 268-300.

The dopamine D3 receptor is a target of pharmacotherapeutic interest in a variety of neurological disorders including schizophrenia, restless leg syndrome, and drug addiction. The high protein sequence homology between the D3 and D2 receptors has posed a challenge to developing D3 receptor-selective ligands whose behavioral actions can be attributed to D3 receptor engagement, in vivo. However, through primarily small molecule structure-activity relationship (SAR) studies, a variety of chemical scaffolds have been discovered over the past two decades that have resulted in

several D3 receptor-selective ligands with high affinity and in vivo activity. Nevertheless, viable clinical candidates remain limited. The recent determination of the high-resolution crystal structure of the D3 receptor has invigorated structure-based drug design, providing refinements to the molecular dynamic models and testable predictions about receptor-ligand interactions. This review will highlight recent preclinical and clinical studies demonstrating potential utility of D3 receptor-selective ligands in the treatment of addiction. In addition, new structure-based rational drug design strategies for D3 receptor-selective ligands that complement traditional small molecule SAR to improve the selectivity and directed efficacy profiles are examined.

## **Designer Drug Research Unit**

**Nonlinear Pharmacokinetics Of (±)-3,4-Methylenedioxymethamphetamine (MDMA) and Its Pharmacodynamic Consequences In the Rat** Concheiro M, Baumann MH, Scheidweiler KB, Rothman RB, Marrone GF, Huestis MA. *Drug Metab Dispos* 2014; 42: 119-125.

3,4-Methylenedioxymethamphetamine (MDMA) is a widely abused illicit drug that can cause severe and even fatal adverse effects. However, interest remains for its possible clinical applications in post-traumatic stress disorder and anxiety treatment. Preclinical studies to determine MDMA's safety are needed. The authors evaluated MDMA pharmacokinetics and metabolism in male rats receiving 2.5, 5 and 10 mg/kg subcutaneous MDMA, and the associated pharmacodynamic consequences. Blood was collected via jugular catheter at 0, 0.5, 1, 2, 4, 6, 8, 16 and 24 h, with simultaneous serotonin (5-HT) behavioral syndrome and core temperature monitoring. Plasma specimens were analyzed for MDMA and metabolites (±)-3,4 dihydroxymethamphetamine (HHMA), (±)-4-hydroxy-3-methoxymethamphetamine (HMMA) and (±)-3,4-methylenedioxyamphetamine (MDA) by liquid chromatography-tandem mass spectrometry. After 2.5 mg/kg MDMA, mean maximum MDMA concentration was 164±47.1 ng/ml, HHMA and HMMA were major metabolites, and <20% MDMA was metabolized to MDA. After 5 and 10 mg/kg doses, MDMA areas-under-the-curve (AUC) were 3- and 10-fold greater than those after 2.5 mg/kg; HHMA and HMMA AUC values were relatively constant across doses, while MDA AUC values were greater than dose proportional. These data provide decisive in vivo evidence that MDMA and MDA display nonlinear accumulation via metabolic auto-inhibition in the rat. Importantly, 5-HT syndrome severity correlated with MDMA concentrations ( $r=0.8083$ ,  $p<0.0001$ ), while core temperature correlated with MDA concentrations ( $r=0.7595$ ,  $p<0.0001$ ), suggesting MDMA's behavioral and hyperthermic effects may involve distinct mechanisms. Given key similarities between MDMA pharmacokinetics in rats and humans, data from rats can be useful when provided at clinically-relevant doses.

**Effects of 3,4-methylenedioxymethamphetamine (MDMA) and its Main Metabolites on Cardiovascular Function in Conscious Rats** Schindler CW, Thorndike EB, Blough BE, Tella SR, Goldberg SR, Baumann MH. *Br. J. Pharmacology* 2014; 171: 83-91.

The cardiovascular effects produced by 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") contribute to its acute toxicity, but the potential role of MDMA metabolites in this regard is not known. Here the authors examined the effects of MDMA metabolites on cardiovascular function in rats. Radiotelemetry was employed to evaluate the effects of subcutaneous (s.c.) administration of racemic MDMA or its phase I metabolites on blood pressure, heart rate and locomotor activity in conscious male rats. MDMA (1-20 mg/kg) produced dose-related increases in blood pressure, heart rate and activity. Peak effects on heart rate occurred at a lower dose than peak effects on blood pressure or activity. The N-demethylated metabolite 3,4-methylenedioxyamphetamine (MDA) produced effects that mimicked MDMA. The metabolite 3,4-dihydroxymethamphetamine (HHMA, 1-10 mg/kg)

increased heart rate more potently and to a greater extent than MDMA, while 3,4-dihydroxyamphetamine increased heart rate, but less than HHMA. Neither dihydroxy metabolite altered motor activity. The metabolites 4-hydroxy-3-methoxymethamphetamine and 4-hydroxy-3-methoxyamphetamine did not affect any parameters. Tachycardia produced by MDMA and HHMA was blocked by the beta-adrenergic antagonist propranolol. These results demonstrate that HHMA may contribute significantly to the cardiovascular effects of MDMA in vivo. As such, determining the molecular mechanism of action for HHMA and other hydroxyl metabolites of MDMA warrants further study.

## Psychobiology Section

**Molecular and Atypical System Effects at the Dopamine Transporter** Hiranita T, Wilkinson DS, Hong WC, Zou M-F, Kopajtic TA, Soto PL, Lupica CR, Newman AH, Katz JL. *Journal of Pharmacology and Experimental Therapeutics*, DOI:10.1124/jpet.113.212738

The present study examined RTI-371 (3 $\beta$ -(4-methylphenyl)-2 $\beta$ -[3-(4-chlorophenyl)-isoxazol-5-yl]tropane), a phenyltropane cocaine analog with effects distinct from cocaine, and assessed potential mechanisms for those effects by comparison with its constitutional isomer, RTI-336 (3 $\beta$ -(4-chlorophenyl)-2 $\beta$ -[3-(4-methylphenyl)-isoxazol-5-yl]tropane). In mice RTI-371 was less effective than cocaine and RTI-336 in stimulating locomotion, and incompletely substituted (~60% maximum at 5-min or 1-hr post-injection) in a cocaine (10 mg/kg, i.p.)/saline discrimination procedure; RTI-336 completely substituted. In contrast to RTI-336, RTI-371 was not self-administered, and its pretreatment (1.0-10 mg/kg, i.p.) dose-dependently decreased maximal cocaine self-administration more potently than food-maintained responding. RTI-336 pretreatment dose-dependently left-shifted the cocaine self-administration dose-effect curve. Both RTI-336 and RTI-371 displaced [3H]WIN35, at serotonin or norepinephrine transporters, or muscarinic and sigma receptors. The relative low affinity at these sites suggests the DAT as the primary target of RTI-371 with minimal contributions from these other targets. In biochemical assays probing the outward-facing DAT conformation, both RTI-371 and RTI-336 had effects similar to cocaine, suggesting little contribution of DAT conformation to the unique pharmacology of RTI-371. The locomotor-stimulant effects of RTI-371 (3.0-30 mg/kg, i.p.) were comparable in CB1R WT and KO mice, indicating that previously reported CB1 allosteric effects do not decrease cocaine-like effects of RTI-371. DAT occupancy in vivo was most rapid with cocaine and least with RTI-371. The slow apparent association rate may allow compensatory actions that in turn dampen cocaine-like stimulation, and give RTI-371 its unique pharmacological profile. 428 binding to striatal dopamine transporters (DATs) with  $K_i$  values of 10.8 and 7.81 nM, respectively, and had lower affinities.

**Pharmacological Characterization of a Dopamine Transporter Ligand that Functions as a Cocaine Antagonist** Desai, RI, Grandy DK, Lupica CR, Katz JL. *Journal of Pharmacology and Experimental Therapeutics*, 2014; 348: 106–115.

An N-butyl analog of benztropine, JHW007 [N-(n-butyl)-3 $\alpha$ -[bis(4'-fluorophenyl)methoxy]-tropane], binds to dopamine transporters (DAT) but has reduced cocaine-like behavioral effects and antagonizes various effects of cocaine. The present study further examined mechanisms underlying these effects. Cocaine dose-dependently increased locomotion, whereas JHW007 was minimally effective but increased activity 24 hours after injection. JHW007 (3-10 mg/kg) dose-dependently and fully antagonized the locomotor-stimulant effects of cocaine (5-60 mg/kg), whereas N-methyl and N-allyl analogs and the dopamine (DA) uptake inhibitor GBR12909 [1-(2-[bis(4-fluorophenyl)methoxy]ethyl)-4-(3-phenylpropyl)piperazine dihydrochloride] stimulated activity and



failed to antagonize effects of cocaine. JHW007 also blocked the locomotor-stimulant effects of the DAT inhibitor GBR12909 but not stimulation produced by the  $\delta$ -opioid agonist SNC 80 [4-[(R)-[(2S,5R)-4-allyl-2,5-dimethylpiperazin-1-yl](3-methoxyphenyl)methyl]-N,N-diethylbenzamide], which increases activity through nondopaminergic mechanisms. JHW007 blocked locomotor-stimulant effects of cocaine in both DA D2- and CB1-receptor knockout and wild-type mice, indicating a lack of involvement of these targets. Furthermore, JHW007 blocked effects of cocaine on stereotyped rearing but enhanced stereotyped sniffing, suggesting that interference with locomotion by enhanced stereotypies is not responsible for the cocaine-antagonist effects of JHW007. Time-course data indicate that administration of JHW007 antagonized the locomotor-stimulant effects of cocaine within 10 minutes of injection, whereas occupancy at the DAT, as determined in vivo, did not reach a maximum until 4.5 hours after injection. The  $\sigma$ 1-receptor antagonist BD 1008 [N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)ethylamine dihydrobromide] blocked the locomotor-stimulant effects of cocaine. Overall, these findings suggest that JHW007 has cocaine-antagonist effects that deviate from its DAT occupancy and that some other mechanism, possibly  $\sigma$ -receptor antagonist activity, may contribute to the cocaine-antagonist effect of JHW007 and like drugs.

### **Preclinical Efficacy of N-substituted Benztropine Analogs as Antagonists of Methamphetamine Self-administration in Rats**

Hiranita T, Kohut SJ, Soto PL, Tanda G, Kopajtic TA, Katz JL. Journal of Pharmacology and Experimental Therapeutics 2014; 348: 174–191.

Atypical dopamine-uptake inhibitors have low abuse potential and may serve as leads for development of cocaine-abuse treatments. Among them, the bztropine (BZT) derivatives, N-butyl (JHW007), N-allyl (AHN2-005), and N-methyl (AHN1-055) analogs of 3 $\alpha$ -[bis(4'-fluorophenyl)methoxy]-tropane dose-dependently decreased cocaine self-administration without effects on food-maintained responding. This study examined selectivity by assessing their effects on self-administration of other drugs. As with cocaine, each BZT analog (1.0-10.0 mg/kg i.p.) dose-dependently decreased maximal self-administration of d-methamphetamine (0.01-0.32 mg/kg/infusion) but was inactive against heroin (1.0-32.0  $\mu$ g/kg/infusion) and ketamine (0.032-1.0 mg/kg/infusion) self-administration. Further, standard dopamine indirect-agonists [WIN35,428 ((-)-3 $\beta$ -(4-fluorophenyl)-tropan-2- $\beta$ -carboxylic acid methyl ester tartrate), d-amphetamine (0.1-1.0 mg/kg i.p., each)] dose-dependently left-shifted self-administration dose-effect curves for d-methamphetamine, heroin, and ketamine. Noncompetitive NMDA-glutamate receptor/channel antagonists [(+)-MK-801 (0.01-0.1 mg/kg i.p.), memantine (1.0-10.0 mg/kg i.p.)] also left-shifted dose-effect curves for d-methamphetamine and ketamine (but not heroin) self-administration. The  $\mu$ -agonists [dl-methadone and morphine (1.0-10.0 mg/kg i.p., each)] dose-dependently decreased maximal self-administration of  $\mu$ -agonists (heroin, remifentanyl) but not d-methamphetamine or ketamine self-administration. The  $\mu$ -agonist-induced decreases were similar to the effects of BZT analogs on stimulant self-administration and effects of food prefeeding on responding maintained by food reinforcement. Radioligand-binding and behavioral studies suggested that inhibition of dopamine transporters and  $\sigma$  receptors were critical for blocking stimulant self-administration by BZT-analogs. Thus, the present results suggest that the effects of BZT analogs on stimulant self-administration are similar to effects of  $\mu$ -agonists on  $\mu$ -agonist self-administration and food prefeeding on food-reinforced responding, which implicates behavioral mechanisms for these effects and further supports development of atypical dopamine uptake inhibitors as medications for stimulant abuse.

### **Methylphenidate and Impulsivity**

Slezak JM, Ricaurte GA, Tallarida RJ, Katz JL. Psychopharmacology 2014; 231: 191–198.

Current formulations of methylphenidate (MPH) used in treatment of attention-deficit/ hyperactivity disorder (ADHD) result in significantly different bioavailability of MPH enantiomers. Daytrana®, a

dl-MPH transdermal patch system, produces higher levels of l-MPH than when dl-MPH is administered orally (e.g., Ritalin®). One potential limitation of increased l-MPH was indicated in a preclinical study showing l-MPH may attenuate effects of d-MPH. The objective of this study was to investigate the interactive effects of MPH enantiomers by (1) assessing drug effects via a preclinical model of "impulsivity" and (2) performing a quantitative dose equivalence analysis of MPH enantiomer interactions. Sprague-Dawley rats were trained to emit either of two responses, one producing an immediate food pellet, the other producing four pellets delivered at increasing delays (0, 8, and 32 s). The percent selection of the larger food amount was graphed as a function of delay with the area under the curve (AUC) assessed. Increases in AUC are consistent with decreases in "impulsivity" (i.e., selection of the smaller, immediate over the larger, delayed reinforcer). Systemic administration of dl-MPH and d-MPH dose-dependently increased AUC, while l-MPH, morphine, and pentobarbital did not alter AUC. An analysis based upon dose equivalence indicated that dl-MPH produced additive effects that were not different from that predicted from effects of the enantiomers administered alone. The present results indicate pharmacologically selective effects in that only drugs prescribed for the treatment of ADHD symptoms decreased a measure of "impulsivity" and that l-MPH likely does not attenuate or enhance the effects of d-MPH in the current delay-discounting task.

## **Clinical Pharmacology and Therapeutics Research Branch**

### **Treatment Section**

**Smartphone Delivery of Mobile HIV Risk Reduction Education** Phillips KA, Epstein DH, Mezghanni M, Vahabzadeh M, Reamer D, Agage D, Preston KL. AIDS Res Treat. 2013;2013:231956. doi: 10.1155/2013/231956. Epub 2013 Sep 17.

The authors sought to develop and deploy a video-based smartphone-delivered mobile HIV Risk Reduction (mHIVRR) intervention to individuals in an addiction treatment clinic. They developed 3 video modules that consisted of a 10-minute HIVRR video, 11 acceptability questions, and 3 knowledge questions and deployed them as a secondary study within a larger study of ecological momentary and geographical momentary assessments. All 24 individuals who remained in the main study long enough completed the mHIVRR secondary study. All 3 videos met a priori criteria for acceptability "as is" in the population: they achieved median scores of  $\leq 2.5$  on a 5-point Likert scale;  $\leq 20\%$  of the individuals gave them the most negative rating on the scale; a majority of the individuals stated that they would not prefer other formats over video-based smartphone-delivered one (all  $P < 0.05$ ). Additionally, all of our video modules met our a priori criteria for feasibility:  $\leq 20\%$  of data were missing due to participant noncompliance and  $\leq 20\%$  were missing due to technical failure. The authors concluded that video-based mHIVRR education delivered via smartphone is acceptable, feasible and may increase HIV/STD risk reduction knowledge. Future studies, with pre-intervention assessments of knowledge and random assignment, are needed to confirm these findings.

**Daily Temporal Patterns of Heroin and Cocaine Use and Craving: Relationship with Business Hours Regardless of Actual Employment Status** Phillips KA, Epstein DH, Preston KL. Addict Behav. 2013 Oct; 38(10): 2485-2491. doi: 10.1016/j.addbeh.2013.05.010. Epub 2013 May 22.

Real-time monitoring of behavior using Ecological Momentary Assessment (EMA) has provided detailed data about daily temporal patterns of craving and use in cigarette smokers. The authors have collected similar data from a sample of cocaine and heroin users. Here they analyzed it in the context of its relationship with a societal construct of daily temporal organization: 9-to-5 business hours. In a 28-week prospective study, 112 methadone-maintained polydrug-abusing individuals initiated an

electronic-diary entry and provided data each time they used cocaine, heroin, or both during weeks 4 to 28. EMA data were collected for 10,781 person-days and included: 663 cocaine-craving events, 710 cocaine-use events, 288 heroin-craving events, 66 heroin-use events, 630 craving-both-drugs events, and 282 use-of-both-drugs events. At baseline, 34% of the participants reported full-time employment in the preceding 3-year period. Most participants' current employment status fluctuated throughout the study. In a generalized linear mixed model (SAS Proc Glimmix), cocaine use varied by time of day relative to business hours ( $p < 0.0001$ ) and there was a significant interaction between Day of the Week and Time Relative to Business Hours ( $p < 0.002$ ) regardless of current work status. Cocaine craving also varied by time of day relative to business hours ( $p < 0.0001$ ), however, there was no significant interaction between Day of the Week and Time Relative to Business Hours ( $p = .57$ ). Heroin craving and use were mostly reported during business hours, but data were sparse. Cocaine craving is most frequent during business hours while cocaine use is more frequent after business hours. Cocaine use during business hours, but not craving, seems suppressed on most weekdays, but not weekends, suggesting that societal conventions reflected in business hours influence drug-use patterns even in individuals whose daily schedules are not necessarily dictated by employment during conventional business hours.

**Real-Time Tracking Of Neighborhood Surroundings and Mood In Urban Drug Misusers: Application Of A New Method To Study Behavior In Its Geographical Context** Epstein DH, Tyburski M, Craig IM, Phillips KA, Jobes ML, Vahabzadeh M, Mezghanni M, Lin JL, Furr-Holden CD, Preston KL. *Drug Alcohol Depend.* 2014 Jan 1; 134: 22-29. doi: 10.1016/j.drugalcdep.2013.09.007. Epub 2013 Sep 14.

Maladaptive behaviors may be more fully understood and efficiently prevented by ambulatory tools that assess people's ongoing experience in the context of their environment. To demonstrate new field-deployable methods for assessing mood and behavior as a function of neighborhood surroundings (geographical momentary assessment; GMA), the authors collected time-stamped GPS data and ecological momentary assessment (EMA) ratings of mood, stress, and drug craving over 16 weeks at randomly prompted times during the waking hours of opioid-dependent polydrug users receiving methadone maintenance. Locations of EMA entries and participants' travel tracks calculated for the 12 hours before each EMA entry were mapped. Associations between subjective ratings and objective environmental ratings were evaluated at the whole neighborhood and 12-h track levels. Participants ( $N = 27$ ) were compliant with GMA data collection; 3711 randomly prompted EMA entries were matched to specific locations. At the neighborhood level, physical disorder was negatively correlated with negative mood, stress, and heroin and cocaine craving ( $ps < .0001-.0335$ ); drug activity was negatively correlated with stress, heroin and cocaine craving ( $ps .0009-.0134$ ). Similar relationships were found for the environments around respondents' tracks in the 12h preceding EMA entries. The results support the feasibility of GMA. The relationships between neighborhood characteristics and participants' reports were counterintuitive and counter-hypothesized, and challenge some assumptions about how ostensibly stressful environments are associated with lived experience and how such environments ultimately impair health. GMA methodology may have applications for development of individual- or neighborhood-level interventions.

## Chemistry and Drug Metabolism Section

**Validation of the Only Commercially Available Immunoassay for Synthetic Cathinones in Urine: Randox Drugs of Abuse V Biochip Array Technology** Ellefsen KN, Anizan S, Castaneto MS, Desrosiers NA, Martin TM, Klette KL, Huestis MA. Drug Testing and Analysis 2014, e-pub March 22, 2014.

Deterrence of synthetic cathinone abuse is hampered by the lack of a high-throughput immunoassay screen. The Randox Drugs of Abuse V (DOA-V) Biochip Array Technology contains two synthetic cathinone antibodies: Bath Salt I (BSI) targets mephedrone/methcathinone and Bath Salt II (BSII) targets 3',4'-methylenedioxypyrovalerone (MDPV)/3',4'-methylenedioxy- $\alpha$ -pyrrolidinobutiophenone (MDPBP). The authors evaluated DOA-V synthetic cathinones performance and conducted a full validation on the original assay with calibrators reconstituted in water, and the new assay with calibrators prepared in lyophilized urine; both utilized the same antibodies and were run on the fully automated Evidence® Analyzer. The authors screened 20,017 authentic military urine specimens and confirmed positives by liquid chromatography-tandem mass spectrometry (LC-MS/MS) for 28 synthetic cathinones. Limits of detection (LOD) for the original and new assays were 0.35 and 0.18 (BSI), and 8.5 and 9.2  $\mu\text{g/L}$  (BSII), respectively. Linearity was acceptable ( $R^2 > 0.98$ ); however, a large negative bias was observed with in-house prepared calibrators. Intra-assay imprecision was  $<20\%$  BSI-II, while inter-assay imprecision was 18-42% BSI and  $<22\%$  BSII. Precision was acceptable for Randox controls. Cross-reactivity's of many additional synthetic cathinones were determined. Authentic drug-free negative urine pH  $<4$  produced false positive results for BSI (6.3  $\mu\text{g/L}$ ) and BSII (473  $\mu\text{g/L}$ ). Oxidizing agents reduced BSI and increased BSII results. Sensitivity, specificity, and efficiency of 100%, 52.1%, and 53.0% were obtained at manufacturer's proposed cut-offs (BSI 5  $\mu\text{g/L}$ , BSII 30  $\mu\text{g/L}$ ). Performance improved if cut-off concentrations increased (BSI 7.5  $\mu\text{g/L}$ , BSII 40  $\mu\text{g/L}$ ); however, there were limited confirmed positive specimens. Currently, this is the first and only fully validated immunoassay for preliminary detection of synthetic cathinones in urine.

**Cannabinoid Disposition in Oral Fluid after Controlled Cannabis Smoking in Frequent and Occasional Smokers** Newmeyer MN, Desrosiers NA, Lee D, Mendu DR, Barnes AJ, Gorelick DA, Huestis MA. Drug Testing and Analysis 2014, e-pub March 20, 2014.

Oral fluid (OF) is an increasingly popular alternative matrix for drug testing, with cannabinoids being the most commonly identified illicit drug. Quantification of multiple OF cannabinoids and understanding differences in OF cannabinoid pharmacokinetics between frequent and occasional smokers improve test interpretation. The new Oral-Eze® OF collection device has an elution buffer that stabilizes analytes and improves drug recovery from the collection pad; however, its performance has not been independently evaluated. After controlled smoking of a 6.8%  $\Delta^9$ -tetrahydrocannabinol (THC) cannabis cigarette by frequent and occasional smokers, OF was collected with the Oral-Eze device for up to 30 h. Samples were analyzed for multiple cannabinoids by a validated 2D-GC-MS method. Frequent smokers had significantly greater OF THCCOOH concentrations than occasional smokers at all times, and showed positive results for a significantly longer time. The authors evaluated multiple cannabinoid cut-offs; the shortest last detection times were observed when  $\text{THC} \geq 1 \mu\text{g/L}$  was combined with  $\text{CBD}$  or  $\text{CBN} \geq 1 \mu\text{g/L}$ . With these cut-offs, last detection times (1-13.5 h) were not significantly different between groups, demonstrating suitability for short-term cannabinoid detection independent of smoking history. Cut-offs utilizing THC alone or combined with THCCOOH showed significantly different last detection times between groups. The widest detection windows were observed with  $\text{THC} \geq 1$  or  $2 \mu\text{g/L}$  or  $\text{THCCOOH} \geq 20 \text{ng/L}$ . These data illustrate the effectiveness of the Oral-Eze® device for OF collection, the impact of self-administered smoked cannabis history on OF cannabinoid results, and the ability to improve interpretation and tailor OF cannabinoid cut-offs to

fulfill the detection window needs of a given program.

**Effects of Prenatal Methamphetamine Exposure on Behavioral and Cognitive Findings at 7.5 Years of Age**

Diaz SD, Smith LM, LaGasse LL, Derauf C, Newman E, Hah R, Arria A, Huestis MA, Della Grotta S, Dansereau LM, Neal C, Lester BM. Journal of Pediatrics 2014, e-pub Mar 12, 2014. The objective of this study was to examine child behavioral and cognitive outcomes after prenatal exposure to methamphetamine. The authors enrolled 412 mother-infant pairs (204 methamphetamine-exposed and 208 unexposed matched comparisons) in the Infant Development, Environment, and Lifestyle study. The 151 children exposed to methamphetamine and 147 comparisons who attended the 7.5-year visit were included. Exposure was determined by maternal self-report and/or positive meconium toxicology. Maternal interviews assessed behavioral and cognitive outcomes using the Conners' Parent Rating Scale-Revised: Short Form. After adjusting for covariates, children exposed to methamphetamine had significantly higher cognitive problems subscale scores than comparisons and were 2.8 times more likely to have cognitive problems scores that were above average on the Conners' Parent Rating Scale-Revised: Short Form. No association between prenatal methamphetamine exposure and behavioral problems, measured by the oppositional, hyperactivity, and attention-deficit/hyperactivity disorder index subscales, were found. The authors conclude that prenatal methamphetamine exposure was associated with increased cognitive problems, which may affect academic achievement and lead to increased negative behavioral outcomes.

**Phase I and II Cannabinoid Disposition in Blood and Plasma of Occasional and Frequent Smokers Following Controlled Smoked Cannabis**

Desrosiers NA, Himes SK, Scheidweiler KB, Concheiro M, Gorelick DA, Huestis MA. Clinical Chemistry 2014, e-pub Feb 21, 2014.  $\Delta^9$ -Tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) have been reported in blood from frequent cannabis smokers for an extended time during abstinence. The authors compared THC, 11-OH-THC, THCCOOH, cannabidiol, cannabinol, THC-glucuronide, and THCCOO-glucuronide blood and plasma disposition in frequent and occasional cannabis smokers. Frequent and occasional smokers resided on a closed research unit and smoked one 6.8% THC cannabis cigarette ad libitum. Blood and plasma cannabinoids were quantified on admission (approximately 19 h before), 1 h before, and up to 15 times (0.5-30 h) after smoking. Cannabinoid blood and plasma concentrations were significantly higher in frequent smokers compared with occasional smokers at most time points for THC and 11-OH-THC and at all time points for THCCOOH and THCCOO-glucuronide. Cannabidiol, cannabinol, and THC-glucuronide were not significantly different at any time point. Overall blood and plasma cannabinoid concentrations were significantly higher in frequent smokers for THC, 11-OH-THC, THCCOOH, and THCCOO-glucuronide, with and without accounting for baseline concentrations. For blood THC  $>5 \mu\text{g/L}$ , median (range) time of last detection was 3.5 h (1.1- $>30$  h) in frequent smokers and 1.0 h (0-2.1 h) in occasional smokers; 2 individuals had no samples with THC  $>5 \mu\text{g/L}$ . The authors conclude that cannabis smoking history plays a major role in cannabinoid detection. These differences may impact clinical and impaired driving drug detection. The presence of cannabidiol, cannabinol, or THC-glucuronide indicates recent use, but their absence does not exclude it.

**Risk of Neurobehavioral Disinhibition in Prenatal Methamphetamine-Exposed Young Children With Positive Hair Toxicology Results**

Himes SK, LaGasse LL, Derauf C, Newman E, Smith LM, Arria AM, Della Grotta SA, Dansereau LM, Abar B, Neal CR, Lester BM, Huestis MA. Therapeutic Drug Monitoring 2014, e-pub Feb 7, 2014.

The objective of this study was to evaluate the effects of prenatal methamphetamine exposure (PME) and postnatal drug exposures identified by child hair analysis on neurobehavioral disinhibition at 6.5

years of age. Mother-infant pairs were enrolled in the Infant Development, Environment, and Lifestyle (IDEAL) Study in Los Angeles, Honolulu, Tulsa, and Des Moines. PME was determined by maternal self-report and/or positive meconium results. At the 6.5-year follow-up visit, hair was collected and analyzed for methamphetamine, tobacco, cocaine, and cannabinoid markers. Child behavioral and executive function test scores were aggregated to evaluate child neurobehavioral disinhibition. Hierarchical linear regression models assessed the impact of PME, postnatal substances, and combined PME with postnatal drug exposures on the child's neurobehavioral disinhibition aggregate score. Past year caregiver substance use was compared with child hair results. A total of 264 children were evaluated. Significantly more PME children (n = 133) had hair positive for methamphetamine/amphetamine (27.1% versus 8.4%) and nicotine/cotinine (38.3% versus 25.2%) than children without PME (n = 131). Overall, no significant differences in analyte hair concentrations were noted between groups. Significant differences in behavioral and executive function were observed between children with and without PME. No independent effects of postnatal methamphetamine or tobacco exposure, identified by positive hair test, were noted and no additional neurobehavioral disinhibition was observed in PME children with postnatal drug exposures, as compared with PME children without postnatal exposure. The authors conclude that child hair testing offered a noninvasive means to evaluate postnatal environmental drug exposure, although no effects from postnatal drug exposure alone were seen. PME, alone and in combination with postnatal drug exposures, was associated with behavioral and executive function deficits at 6.5 years.

**Quantification of 11-Nor-9-Carboxy- $\Delta$ 9-Tetrahydrocannabinol in Human Oral Fluid by Gas Chromatography-Tandem Mass Spectrometry**

Barnes AJ, Scheidweiler KB, Huestis MA. Therapeutic Drug Monitoring. 2014 Apr; 36(2): 225-233.

A sensitive and specific method for the quantification of 11-nor-9-carboxy- $\Delta$ 9-tetrahydrocannabinol (THCCOOH) in oral fluid collected with the Quantisal and Oral-Eze devices was developed and fully validated. Extracted analytes were derivatized with hexafluoroisopropanol and trifluoroacetic anhydride and quantified by gas chromatography-tandem mass spectrometry with negative chemical ionization. Standard curves, using linear least-squares regression with 1/x weighting were linear from 10 to 1000 ng/L with coefficients of determination >0.998 for both collection devices. Bias was 89.2%-112.6%, total imprecision 4.0%-5.1% coefficient of variation, and extraction efficiency >79.8% across the linear range for Quantisal-collected specimens. Bias was 84.6%-109.3%, total imprecision 3.6%-7.3% coefficient of variation, and extraction efficiency >92.6% for specimens collected with the Oral-Eze device at all 3 quality control concentrations (10, 120, and 750 ng/L). This effective high-throughput method reduces analysis time by 9 minutes per sample compared with our current 2-dimensional gas chromatography-mass spectrometry method and extends the capability of quantifying this important oral fluid analyte to gas chromatography-tandem mass spectrometry. This method was applied to the analysis of oral fluid specimens collected from individuals participating in controlled cannabis studies and will be effective for distinguishing passive environmental contamination from active cannabis smoking.

**Validation of a Novel Method to Identify In Utero Ethanol Exposure: Simultaneous Meconium Extraction of Fatty Acid Ethyl Esters, Ethyl Glucuronide, and Ethyl Sulfate Followed by LC-MS/MS Quantification**

Himes SK, Concheiro M, Scheidweiler KB, Huestis MA. Analytical Bioanalytical Chemistry. 2014, Mar; 406(7): 1945-1955.

Presence of fatty acid ethyl esters (FAEE), ethyl glucuronide (EtG), and ethyl sulfate (EtS) in meconium, the first neonatal feces, identifies maternal alcohol consumption during pregnancy. Current meconium alcohol marker assays require separate analyses for FAEE and EtG/EtS. The authors describe development and validation of the first quantitative liquid chromatography tandem mass

spectrometry assay for 9 FAEEs, EtG, and EtS in 100 mg meconium. For the first time, these alcohol markers are analyzed in the same meconium aliquot, enabling comparison of the efficiency of gestational ethanol exposure detection. 100 mg meconium was homogenized in methanol and centrifuged. The supernatant was divided, and applied to two different solid phase extraction columns for optimized analyte recovery. Limits of quantification for ethyl laurate, myristate, linolenate, palmitoleate, arachidonate, linoleate, palmitate, oleate, and stearate ranged from 25-50 ng/g, with calibration curves to 2,500-5,000 ng/g. EtG and EtS linear dynamic ranges were 5-1,000 and 2.5-500 ng/g, respectively. Mean bias and between-day imprecision were <15 %. Extraction efficiencies were 51.2-96.5 %. Matrix effects ranged from -84.7 to 16.0 %, but were compensated for by matched deuterated internal standards when available. All analytes were stable (within  $\pm 20$  % change from baseline) in 3 authentic positive specimens, analyzed in triplicate, after 3 freeze/thaw cycles (-20 °C). Authentic EtG and EtS also were stable after 12 h at room temperature and 72 h at 4 °C; some FAEE showed instability under these conditions, although there was large inter-subject variability. This novel method accurately detects multiple alcohol meconium markers and enables comparison of markers for maternal alcohol consumption.

**Prenatal Methamphetamine Exposure and Neurodevelopmental Outcomes in Children from 1 to 3 years**

Wouldes TA, LaGasse L, Huestis MA, Della Grotta S, Dansereau L, Lester BM. Neurotoxicology and Teratology. 2014, Feb 22; 42C:77-84.

Despite the evidence that women world-wide are using methamphetamine (MA) during pregnancy little is known about the neurodevelopment of their children. The controlled, prospective longitudinal New Zealand (NZ) Infant Development, Environment and Lifestyle (IDEAL) study was carried out in Auckland, NZ. Participants were 103 children exposed to MA prenatally and 107 who were not exposed. The Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) of the Bayley Scales of Infant Development, Second Edition (BSID-II) measured cognitive and motor performances at ages 1, 2 and 3, and the Peabody Developmental Motor Scale, Second Edition (PDMS-II) measured gross and fine motor performances at 1 and 3. Measures of the child's environment included the Home Observation of Measurement of the Environment and the Maternal Lifestyle Interview. The Substance Use Inventory measured maternal drug use. After controlling for other drug use and contextual factors, prenatal MA exposure was associated with poorer motor performance at 1 and 2 years on the BSID-II. No differences were observed for cognitive development (MDI). Relative to non-MA exposed children, longitudinal scores on the PDI and the gross motor scale of the PDMS-2 were 4.3 and 3.2 points lower, respectively. Being male and of Maori descent predicted lower cognitive scores (MDI) and being male predicted lower fine motor scores (PDMS-2). The authors conclude that prenatal exposure to MA was associated with delayed gross motor development over the first 3 years, but not with cognitive development. However, being male and of Maori descent were both associated with poorer cognitive outcomes. Males in general did more poorly on tasks related to fine motor development.

**Metabolism of Synthetic Cannabinoids PB-22 and its 5-Fluoro Analog, 5F-PB-22, by Human Hepatocyte Incubation and High-Resolution Mass Spectrometry**

Wohlfarth A, Gandhi AS, Pang S, Zhu M, Scheidweiler KB, Huestis, MA. Analytical and Bioanalytical Chemistry. 2014, Feb; 406(6): 1763-1780.

PB-22 (1-pentyl-8-quinolinyl ester-1H-indole-3-carboxylic acid) and 5F-PB-22 (1-(5-fluoropentyl)-8-quinolinyl ester-1H-indole-3-carboxylic acid) are new synthetic cannabinoids with a quinoline substructure and the first marketed substances with an ester bond linkage. No human metabolism data are currently available, making it difficult to document PB-22 and 5F-PB-22 intake from urine analysis, and complicating assessment of the drugs' pharmacodynamic and toxicological properties.

The authors incubated 10  $\mu\text{mol/l}$  PB-22 and 5F-PB-22 with pooled cryopreserved human hepatocytes up to 3 h and analyzed samples on a TripleTOF 5600+ high-resolution mass spectrometer. Data were acquired via TOF scan, followed by information-dependent acquisition triggered product ion scans with mass defect filtering (MDF). The accurate mass full scan MS and MS/MS metabolite datasets were analyzed with multiple data processing techniques, including MDF, neutral loss and product ion filtering. The predominant metabolic pathway for PB-22 and 5F-PB-22 was ester hydrolysis yielding a wide variety of (5-fluoro)pentylindole-3-carboxylic acid metabolites. Twenty metabolites for PB-22 and 22 metabolites for 5F-PB-22 were identified, with the majority generated by oxidation with or without glucuronidation. For 5F-PB-22, oxidative defluorination occurred forming PB-22 metabolites. Both compounds underwent epoxide formation followed by internal hydrolysis and also produced a cysteine conjugate. The authors conclude that human hepatic metabolic profiles were generated for PB-22 and 5F-PB-22. Pentylindole-3-carboxylic acid, hydroxypentyl-PB-22 and PB-22 pentanoic acid for PB-22, and 5'-fluoropentylindole-3-carboxylic acid, PB-22 pentanoic acid and the hydroxy-5F-PB-22 metabolite with oxidation at the quinoline system for 5F-PB-22 are likely the best targets to incorporate into analytical methods for urine to document PB-22 and 5F-PB-22 intake.

**Simultaneous Quantification of 20 Synthetic Cannabinoids and 21 Metabolites, and Semi-quantification of 12 Alkyl Hydroxy Metabolites in Human Urine by Liquid Chromatography-Tandem Mass Spectrometry** Scheidweiler KB, Huestis MA. Journal of Chromatography A. 2014 Jan 31; 1327: 105-117.

Clandestine laboratories constantly produce new synthetic cannabinoids to circumvent legislative efforts, complicating toxicological analysis. No extensive synthetic cannabinoid quantitative urinary methods are reported in the literature. The authors developed and validated a liquid chromatography-tandem mass spectrometric (LC-MS/MS) method for simultaneously quantifying JWH-018, JWH-019, JWH-073, JWH-081, JWH-122, JWH-200, JWH-210, JWH-250, JWH-398, RCS-4, AM-2201, MAM-2201, UR-144, CP 47,497-C7, CP 47,497-C8 and their metabolites, and JWH-203, AM-694, RCS-8, XLR-11 and HU-210 parent compounds in urine. Non-chromatographically resolved alkyl hydroxy metabolite isomers were considered semi-quantitative.  $\beta$ -Glucuronidase hydrolyzed urine was extracted with 1ml Biotage SLE+ columns. Specimens were reconstituted in 150 $\mu\text{L}$  mobile phase consisting of 50% A (0.01% formic acid in water) and 50% B (0.01% formic acid in 50:50 methanol:acetonitrile). 4 and 25 $\mu\text{L}$  injections were performed to acquire data in positive and negative ionization modes, respectively. The LC-MS/MS instrument consisted of a Shimadzu UFLCxr system and an ABSciex 5500 Qtrap mass spectrometer with an electrospray source. Gradient chromatographic separation was achieved utilizing a Restek Ultra Biphenyl column with a 0.5ml/min flow rate and an overall run time of 19.5 and 11.4min for positive and negative mode methods, respectively. Quantification was by multiple reaction monitoring with CP 47,497 compounds and HU-210 ionized via negative polarity; all other analytes were acquired in positive mode. Lower and upper limits of linearity were 0.1-1.0 and 50-100 $\mu\text{g/l}$  ( $r(2)>0.994$ ). Validation parameters were evaluated at three concentrations spanning linear dynamic ranges. Inter-day analytical recovery (bias) and imprecision ( $N=20$ ) were 88.3-112.2% and 4.3-13.5% coefficient of variation, respectively. Extraction efficiencies and matrix effect ( $N=10$ ) were 44-110 and -73 to 52%, respectively. The authors present a novel LC-MS/MS method for simultaneously quantifying 20 synthetic cannabinoids and 21 metabolites, and semi-quantifying 12 alkyl hydroxy metabolites in urine.



**In Vitro Stability of Free and Glucuronidated Cannabinoids in Urine Following Controlled Smoked Cannabis** Desrosiers NA, Lee D, Scheidweiler KB, Concheiro M, Gorelick DA, Huestis MA. Analytical and Bioanalytical Chemistry 2014 Jan; 406(3): 785-792.

Analyte stability is an important factor in urine test interpretation, yet cannabinoid stability data are limited. A comprehensive study of  $\Delta(9)$ -tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), 11-nor-9-carboxy-THC (THCCOOH), cannabidiol, cannabinol, THC-glucuronide, and THCCOOH-glucuronide stabilities in authentic urine was completed. Urine samples after ad libitum cannabis smoking were pooled to prepare low and high pools for each study participant; baseline concentrations were measured within 24 h at room temperature (RT), 4 °C and -20 °C. Stability at RT, 4 °C and -20 °C was evaluated by Friedman tests for up to 1 year. THCCOOH, THC-glucuronide, and THCCOOH-glucuronide were quantified in baseline pools. RT THCCOOH baseline concentrations were significantly higher than -20 °C, but not 4 °C baseline concentrations. After 1 week at RT, THCCOOH increased, THCCOOH-glucuronide decreased, but THC-glucuronide was unchanged. In RT low pool, total THCCOOH (THCCOOH + THCCOOH-glucuronide) was significantly lower after 1 week. At 4 °C, THCCOOH was stable 2 weeks, THCCOOH-glucuronide 1 month and THC-glucuronide for at least 6 months. THCCOOH was stable frozen for 1 year, but 6 months high pool results were significantly higher than baseline; THC-glucuronide and THCCOOH-glucuronide were stable for 6 months. Total THCCOOH was stable 6 months at 4 °C, and frozen 6 months (low) and 1 year (high). THC, cannabidiol and cannabinol were never detected in urine; although not detected initially, 11-OH-THC was detected in 2 low and 3 high pools after 1 week at RT. Substantial THCCOOH-glucuronide deconjugation was observed at RT and 4 °C. Analysis should be conducted within 3 months if non-hydrolyzed THCCOOH or THCCOOH-glucuronide quantification is required.

**Rimonabant Effects on Anxiety Induced by Simulated Public Speaking in Healthy Humans: a Preliminary Report** Bergamaschi MM, Queiroz RHC, Chagas MHN, Linares IMP, Arrais KC, Oliveira DCG, Queiroz ME, Nardi AE, Huestis MA, Hallak JEC, Zuardi AW, Moreira FA, Crippa JAS. Human Psychopharmacology: Clinical and Experimental. 2014 Jan; 29(1): 94-99.

The authors investigated the hypothesis that rimonabant, a cannabinoid antagonist/inverse agonist, would increase anxiety in healthy subjects during a simulation of the public speaking test. Participants were randomly allocated to receive oral placebo or 90mg rimonabant in a double-blind design. Subjective effects were measured by Visual Analogue Mood Scale. Physiological parameters, namely arterial blood pressure and heart rate, also were monitored. Twelve participants received oral placebo and 12 received 90mg rimonabant. Rimonabant increased self-reported anxiety levels during the anticipatory speech and performance phase compared with placebo. Interestingly, rimonabant did not modulate anxiety prestress and was not associated with sedation, cognitive impairment, discomfort, or blood pressure changes. The authors conclude that cannabinoid-1 antagonism magnifies the responses to an anxiogenic stimulus without interfering with the prestress phase. These data suggest that the endocannabinoid system may work on-demand to counteract the consequences of anxiogenic stimuli in healthy humans.

**Psychiatric Symptom Differences in People with Schizophrenia Associated with Substantial Lifetime Substance Use but No Current Substance Use Disorder** Koola MM, Gorelick DA, McMahon RP, Liu F, Huestis MA, Linthicum J, Feldman SM, Warren KR, Wehring HJ, Kelly DL. Schizophrenia Research. 2014 Jan; 152(1): 315-316.

People with schizophrenia who have current substance use disorder (SUD) are generally excluded from clinical trials for the following reasons: safety/side effect risk, concern about adherence to the study protocol and avoidance of confounds to efficacy evaluations. Patients with a past history of SUD are generally not excluded, but may represent a population with similar potentially unfavorable

characteristics. To evaluate the possible consequences of this differential exclusion practice, the authors examined baseline symptoms of participants with substantial lifetime substance use and compared to participants with no substantial lifetime substance use in a sample of 15 outpatients with schizophrenia or schizoaffective disorder (DSM-IV criteria) enrolled in a controlled clinical trial of an adjunct weight loss medication. There were no significant differences in participants' sociodemographic characteristics. Both patient groups were comparable in demographic characteristics and cigarette smoking. The ten participants with substantial lifetime substance use had more severe positive symptoms and less severe negative symptoms than the five participants without a substantial history of substance use. Future studies are warranted with larger sample sizes, objective assessments of substance use, and clear distinctions between substance use groups. Persisting effects from prior substance use may adversely affect response to treatment, leading clinicians to add or change medications, when a more appropriate action might be evaluation of prior substance use. In addition, prior substance use is a risk factor for relapse to present substance use or abuse, with potential adverse effects on current treatment response.

## **Molecular Neuropsychiatry Research Branch**

### **Incubation of Methamphetamine and Palatable Food Craving after Punishment-Induced**

**Abstinence** Krasnova IN, Marchant NJ, Ladenheim B, McCoy MT, Panlilio LV, Bossert JM, Shaham Y, Cadet JL. Neuropsychopharmacology. 2014 Mar 3. doi: 10.1038/npp.2014.50. [Epub ahead of print]

In a rat model of drug craving and relapse, cue-induced drug seeking progressively increases after withdrawal from methamphetamine and other drugs, a phenomenon termed 'incubation of drug craving'. However, current experimental procedures used to study incubation of drug craving do not incorporate negative consequences of drug use, which is a common factor promoting abstinence in humans. Here, the authors studied whether incubation of methamphetamine craving is observed after suppression of drug seeking by adverse consequences (punishment). They trained rats to self-administer methamphetamine or palatable food for 9-h per day for 14 days; reward delivery was paired with a tone-light cue. Subsequently, for one group within each reward type, 50% of the lever-presses were punished by mild footshock for 9-10 days, while for the other group lever-presses were not punished. Shock intensity was gradually increased over time. Next, we assessed cue-induced reward seeking in 1-h extinction sessions on withdrawal days 2 and 21. Response-contingent punishment suppressed extended-access methamphetamine or food self-administration; surprisingly, food-trained rats showed greater resistance to punishment than methamphetamine-trained rats. During the relapse tests, both punished and unpunished methamphetamine- and food-trained rats showed significantly higher cue-induced reward seeking on withdrawal day 21 than on day 2. These results demonstrate that incubation of both methamphetamine and food craving occur after punishment-induced suppression of methamphetamine or palatable food self-administration. Our procedure can be used to investigate mechanisms of relapse to drug and palatable food seeking under conditions that more closely approximate the human condition.

### **Modafinil Improves Methamphetamine-induced Object Recognition Deficits and Restores Prefrontal Cortex ERK Signaling in Mice**

González B, Raineri M, Cadet JL, García-Rill E, Urbano FJ, Bisagno V. Neuropharmacology. 2014 Feb 12. pii: S0028-3908(14)00055-0. doi: 10.1016/j.neuropharm.2014.02.002. [Epub ahead of print].

Chronic use of methamphetamine (METH) leads to long-lasting cognitive dysfunction in humans and in animal models. Modafinil is a wake-promoting compound approved for the treatment of sleeping

disorders. It is also prescribed off label to treat METH dependence. In the present study, the authors investigated whether modafinil could improve cognitive deficits induced by sub-chronic METH treatment in mice by measuring visual retention in a Novel Object Recognition (NOR) task. After sub-chronic METH treatment (1 mg/kg, once a day for 7 days), mice performed the NOR task, which consisted of habituation to the object recognition arena (5 min a day, 3 consecutive days), training session (2 equal objects, 10 min, day 4), and a retention session (1 novel object, 5 min, day 5). One hour before the training session, mice were given a single dose of modafinil (30 or 90 mg/kg). METH-treated mice showed impairments in visual memory retention, evidenced by equal preference of familiar and novel objects during the retention session. The lower dose of modafinil (30 mg/kg) had no effect on visual retention scores in METH-treated mice, while the higher dose (90 mg/kg) rescued visual memory retention to control values. The authors also measured extracellular signal-regulated kinase (ERK) phosphorylation in medial prefrontal cortex (mPFC), hippocampus, and nucleus accumbens (NAc) of METH- and vehicle-treated mice that received modafinil 1 h before exposure to novel objects in the training session, compared to mice placed in the arena without objects. Elevated ERK phosphorylation was found in the mPFC of vehicle-treated mice, but not in METH-treated mice, exposed to objects. The lower dose of modafinil had no effect on ERK phosphorylation in METH-treated mice, while 90 mg/kg modafinil treatment restored the ERK phosphorylation induced by novelty in METH-treated mice to values comparable to controls. The authors found neither a novelty nor treatment effect on ERK phosphorylation in hippocampus or NAc of vehicle- and METH-treated mice receiving acute 90 mg/kg modafinil treatment. These results showed a palliative role of modafinil against METH-induced visual cognitive impairments, possibly by normalizing ERK signaling pathways in mPFC. Modafinil may be a valuable pharmacological tool for the treatment of cognitive deficits observed in human METH abusers as well as in other neuropsychiatric conditions.

**Enhanced Upregulation of CRH mRNA Expression in the Nucleus Accumbens of Male Rats after a Second Injection of Methamphetamine Given Thirty Days Later**

Cadet JL, Brannock C, Ladenheim B, McCoy MT, Krasnova IN, Lehrmann E, Becker KG, Jayanthi S. PLoS One. 2014 Jan 27;9(1):e84665. doi: 10.1371/journal.pone.0084665. eCollection 2014.

Methamphetamine (METH) is a widely abused amphetamine analog. Few studies have investigated the molecular effects of METH exposure in adult animals. Herein, the authors determined the consequences of an injection of METH (10 mg/kg) on transcriptional effects of a second METH (2.5 mg/kg) injection given one month later. They thus measured gene expression by microarray analyses in the nucleus accumbens (NAc) of 4 groups of rats euthanized 2 hours after the second injection: saline-pretreated followed by saline-challenged (SS) or METH-challenged (SM); and METH-pretreated followed by saline-challenged (MS) or METH-challenged (MM). Microarray analyses revealed that METH (2.5 mg/kg) produced acute changes (1.8-fold;  $P < 0.01$ ) in the expression of 412 (352 upregulated, 60 down-regulated) transcripts including cocaine and amphetamine regulated transcript, corticotropin-releasing hormone (Crh), oxytocin (Oxt), and vasopressin (Avp) that were upregulated. Injection of METH (10 mg/kg) altered the expression of 503 (338 upregulated, 165 down-regulated) transcripts measured one month later (MS group). These genes also included Cart and Crh. The MM group showed altered expression of 766 (565 upregulated, 201 down-regulated) transcripts including Avp, Cart, and Crh. The METH-induced increased Crh expression was enhanced in the MM group in comparison to SM and MS groups. Quantitative PCR confirmed the METH-induced changes in mRNA levels. Therefore, a single injection of METH produced long-lasting changes in gene expression in the rodent NAc. The long-term increases in Crh, Cart, and Avp mRNA expression suggest that METH exposure produced prolonged activation of the endogenous stress system. The METH-induced changes in oxytocin expression also suggest the possibility that this neuropeptide might play a significant role in the neuroplastic and affiliative effects of this drug.

**The Primacy of Cognition in the Manifestations of Substance Use Disorders** Cadet JL, Bisagno V. Front Neurol. 2013 Nov 18;4:189. eCollection 2013. Review.

Drug addiction is a serious public health problem that consists of a compulsive drive to take drugs despite repeated severe adverse consequences. Factors that influence the development and maintenance of addiction include access to drugs, social environment, genetic predisposition, and psychiatric comorbidities. Even in the absence of specific psychiatric diagnoses, certain psychological vulnerabilities may serve as substrates compounding the initiation of drug use and the development of substance use disorders. For example, individual who are sensation-seekers, impulsive, or behavioral disinhibited appear more prone to develop addiction to both licit and illicit substances. In this context, it is to be noted that not all individuals who try these drugs become addicted as about only 20% of people who have tried drugs become addicts. It is also worth mentioning that repeated exposure to moderate to large doses of some of these illicit drugs may be associated with well-known neuropathological consequences that might not be either necessary or sufficient for the development and the maintenance of addicted states. The accumulated evidence supports the view that a large number of substance users suffer from significant neuropsychological impairments. Neuroimaging studies in drug-dependent individuals have also documented significant functional and structural alterations in several brain regions. These regions include mesocortical, mesolimbic, and mesostriatal brain regions that are known to be impacted by administration of licit and illicit drugs in both clinical and preclinical studies. In what follows, the authors discuss the potential impact of illicit drugs on these brain regions and the associated cognitive consequences of these drugs. They then suggest that these cognitive consequences play primary roles in the maintenance of addiction across several classes of abused substances.

**Neuropathology of Substance Use Disorders** Cadet JL, Bisagno V, Milroy CM. Acta Neuropathol. 2014 Jan;127(1):91-107. doi: 10.1007/s00401-013-1221-7. Epub 2013 Nov 29.

Addictions to licit and illicit drugs are chronic relapsing brain disorders that affect circuits that regulate reward, motivation, memory, and decision-making. Drug-induced pathological changes in these brain regions are associated with characteristic enduring behaviors that continue despite adverse biopsychosocial consequences. Repeated exposure to these substances leads to egocentric behaviors that focus on obtaining the drug by any means and on taking the drug under adverse psychosocial and medical conditions. Addiction also includes craving for the substances and, in some cases, involvement in risky behaviors that can cause death. These patterns of behaviors are associated with specific cognitive disturbances and neuroimaging evidence for brain dysfunctions in a diverse population of drug addicts. Postmortem studies have also revealed significant biochemical and/or structural abnormalities in some addicted individuals. The present review provides a summary of the evidence that has accumulated over the past few years to implicate brain dysfunctions in the varied manifestations of drug addiction. The authors thus review data on cerebrovascular alterations, brain structural abnormalities, and postmortem studies of patients who abuse cannabis, cocaine, amphetamines, heroin, and "bath salts". They also discuss potential molecular, biochemical, and cellular bases for the varied clinical presentations of these patients. Elucidation of the biological bases of addiction will help to develop better therapeutic approaches to these patient populations.

## Chemical Biology Research Branch

### Drug Design and Synthesis Section

#### **Cocaine Dysregulates Opioid Gating of GABA Neurotransmission in the Ventral Pallidum**

Kupchik YM, Scofield MD, Rice KC, Cheng K, Roques BP, Kalivas PW. J Neurosci. 2014; 34(3): 1057-1066.

The ventral pallidum (VP) is a target of dense nucleus accumbens projections. Many of these projections coexpress GABA and the neuropeptide enkephalin, a  $\delta$  and  $\mu$  opioid receptor (MOR) ligand. Of these two, the MOR in the VP is known to be involved in reward-related behaviors, such as hedonic responses to palatable food, alcohol intake, and reinstatement of cocaine seeking. Stimulating MORs in the VP decreases extracellular GABA, indicating that the effects of MORs in the VP on cocaine seeking are via modulating GABA neurotransmission. Here, the authors use whole-cell patch-clamp on a rat model of withdrawal from cocaine self-administration to test the hypothesis that MORs presynaptically regulate GABA transmission in the VP and that cocaine withdrawal changes the interaction between MORs and GABA. They found that in cocaine-extinguished rats pharmacological activation of MORs no longer presynaptically inhibited GABA release, whereas blocking the MORs disinhibited GABA release. Moreover, MOR-dependent long-term depression of GABA neurotransmission in the VP was lost in cocaine-extinguished rats. Last, GABA neurotransmission was found to be tonically suppressed in cocaine-extinguished rats. These substantial synaptic changes indicated that cocaine was increasing tone on MOR receptors. Accordingly, increasing endogenous tone by blocking the enzymatic degradation of enkephalin inhibited GABA neurotransmission in yoked saline rats but not in cocaine-extinguished rats. In conclusion, these results indicate that following withdrawal from cocaine self-administration enkephalin levels in the VP are elevated and the opioid modulation of GABA neurotransmission is impaired. This may contribute to the difficulties withdrawn addicts experience when trying to resist relapse.

#### **Pain-related Depression of the Mesolimbic Dopamine System in Rats: Expression, Blockade by Analgesics, and Role of Endogenous $\kappa$ -opioids**

Leitl MD, Onvani S, Bowers MS, Cheng K, Rice KC, Carlezon WA Jr, Banks ML, Negus SS. Neuropsychopharmacology 2014; 39(3): 614-624.

Pain is often associated with depression of behavior and mood, and relief of pain-related depression is a common goal of treatment. This study tested the hypothesis that pain-related behavioral depression is mediated by activation of endogenous  $\kappa$ -opioid systems and subsequent depression of mesolimbic dopamine release. Adult male Sprague-Dawley rats were implanted with electrodes targeting the medial forebrain bundle (for behavior studies of intracranial self-stimulation (ICSS)) or with cannulae for microdialysis measures of nucleus accumbens dopamine (NAc DA). Changes in ICSS and NAc DA were examined after treatment with a visceral noxious stimulus (intraperitoneal injection of dilute lactic acid) or an exogenous  $\kappa$ -agonist (U69593). Additional studies examined the sensitivity of acid and U69593 effects to blockade by two analgesics (the nonsteroidal antiinflammatory drug ketoprofen and the  $\mu$ -opioid agonist morphine) or by the  $\kappa$ -antagonist norbinaltorphimine (norBNI). The effects of acid were also examined on mRNA expression for prodynorphin (PDYN) and  $\kappa$ -opioid receptors (KORs) in mesocorticolimbic brain regions. Both acid and U69593 depressed ICSS and extracellular levels of NAc DA. Pain-related acid effects were blocked by ketoprofen and morphine but not by norBNI. The U69593 effects were blocked by norBNI but not by ketoprofen, and were only attenuated by morphine. Acid did not significantly alter PDYN or KOR in NAc, but it produced a delayed increase in PDYN in prefrontal cortex. These results support a key role for the mesolimbic DA system, but a more nuanced role for endogenous  $\kappa$ -opioid systems, in mediating acute pain-related behavioral depression in rats.

**Facial Recognition of Heroin Vaccine Opiates: Type 1 Cross-reactivities of Antibodies Induced by Hydrolytically Stable Haptenic Surrogates of Heroin, 6-acetylmorphine, and Morphine**

Matyas GR, Rice KC, Cheng K, Li F, Antoline JF, Iyer MR, Jacobson AE, Mayorov AV, Beck Z, Torres OB, Alving CR. Vaccine 2014; 32(13): 1473-1479.

Novel synthetic compounds similar to heroin and its major active metabolites, 6-acetylmorphine and morphine, were examined as potential surrogate haptens for the ability to interface with the immune system for a heroin vaccine. Recent studies have suggested that heroin-like haptens must degrade hydrolytically to induce independent immune responses both to heroin and to the metabolites, resulting in antisera containing mixtures of antibodies (type 2 cross-reactivity). To test this concept, two unique hydrolytically stable haptens were created based on presumed structural facial similarities to heroin or to its active metabolites. After conjugation of a heroin-like hapten (DiAmHap) to tetanus toxoid and mixing with liposomes containing monophosphoryl lipid A, high titers of antibodies after two injections in mice had complementary binding sites that exhibited strong type 1 ("true") specific cross-reactivity with heroin and with both of its physiologically active metabolites. Mice immunized with each surrogate hapten exhibited reduced antinociceptive effects caused by injection of heroin. This approach obviates the need to create hydrolytically unstable synthetic heroin-like compounds to induce independent immune responses to heroin and its active metabolites for vaccine development. Facial recognition of hydrolytically stable surrogate haptens by antibodies together with type 1 cross-reactivities with heroin and its metabolites can help to guide synthetic chemical strategies for efficient development of a heroin vaccine.

**Systemic Administration of Propentofylline, Ibudilast, and (+)-Naltrexone Each Reverses Mechanical Allodynia in a Novel Rat Model of Central Neuropathic Pain**

Ellis A, Wieseler J, Favret J, Johnson KW, Rice KC, Maier SF, Falci S, Watkins LR. J.Pain 2014, e-pub Jan 9, 2014.

Central neuropathic pain (CNP) is a debilitating consequence of central nervous system damage for which current treatments are ineffective. To explore mechanisms underlying CNP, the authors developed a rat model involving T13/L1 dorsal root avulsion. The resultant dorsal horn damage creates bilateral below-level (L4-L6) mechanical allodynia. This allodynia, termed spinal neuropathic avulsion pain, occurs in the absence of confounding paralysis. To characterize this model, the authors undertook a series of studies aimed at defining whether spinal neuropathic avulsion pain could be reversed by any of 3 putative glial activation inhibitors, each with distinct mechanisms of action. Indeed, the phosphodiesterase inhibitor propentofylline, the macrophage migration inhibitory factor inhibitor ibudilast, and the toll-like receptor 4 antagonist (+)-naltrexone each reversed below-level allodynia bilaterally. Strikingly, none of these impacted spinal neuropathic avulsion pain upon first administration but required 1 to 2 weeks of daily administration before pain reversal was obtained. Given reversal of CNP by each of these glial modulatory agents, these results suggest that glia contribute to the maintenance of such pain and enduring release of macrophage migration inhibitory factor and endogenous agonists of toll-like receptor 4 is important for sustaining CNP. The markedly delayed efficacy of all 3 glial modulatory drugs may prove instructive for interpretation of apparent drug failures after shorter dosing regimens. CNP that develops after trauma is often described by patients as severe and intolerable. Unfortunately, current treatments are not effective. This work suggests that using pharmacologic treatments that target glial cells could be an effective clinical treatment for CNP.

### **Presynaptic Glycine Receptors as a Potential Therapeutic Target for Hyperekplexia Disease**

Xiong W, Chen SR, He L, Cheng K, Zhao YL, Chen H, Li DP, Homanics GE, Peever J, Rice KC, Wu LG, Pan HL, Zhang L. *Nat Neurosci.* 2014; 17(2): 232-239.

Although postsynaptic glycine receptors (GlyRs) as  $\alpha\beta$  heteromers attract considerable research attention, little is known about the role of presynaptic GlyRs, likely  $\alpha$  homomers, in diseases. Here, the authors demonstrate that dehydroxycannabidiol (DH-CBD), a nonpsychoactive cannabinoid, can rescue GlyR functional deficiency and exaggerated acoustic and tactile startle responses in mice bearing point mutations in  $\alpha 1$  GlyRs that are responsible for a hereditary startle-hyperekplexia disease. The GlyRs expressed as  $\alpha 1$  homomers either in HEK-293 cells or at presynaptic terminals of the calyceal synapses in the auditory brainstem are more vulnerable than heteromers to hyperekplexia mutation-induced impairment. Homomeric mutants are more sensitive to DH-CBD than are heteromers, suggesting presynaptic GlyRs as a primary target. Consistent with this idea, DH-CBD selectively rescues impaired presynaptic GlyR activity and diminished glycine release in the brainstem and spinal cord of hyperekplexic mutant mice. Thus, presynaptic  $\alpha 1$  GlyRs emerge as a potential therapeutic target for dominant hyperekplexia disease and other diseases with GlyR deficiency.

### **Innate Immune Factors Modulate Ethanol Interaction with GABAergic Transmission in Mouse Central Amygdala**

Bajo M, Madamba SG, Roberto M, Blednov YA, Sagi VN, Roberts E, Rice KC, Harris RA, Siggins, GR. *Brain Behav. Immun.* 2014, e-pub March 24, 2014.

Excessive ethanol drinking in rodent models may involve activation of the innate immune system, especially toll-like receptor 4 (TLR4) signaling pathways. The authors used intracellular recording of evoked GABAergic inhibitory postsynaptic potentials (eIPSPs) in central amygdala (CeA) neurons to examine the role of TLR4 activation by lipopolysaccharide (LPS) and deletion of its adapter protein CD14 in acute ethanol effects on the GABAergic system. Ethanol (44, 66 or 100 mM) and LPS (25 and 50  $\mu\text{g/ml}$ ) both augmented eIPSPs in CeA of wild type (WT) mice. Ethanol (44 mM) decreased paired-pulse facilitation (PPF), suggesting a presynaptic mechanism of action. Acute LPS (25  $\mu\text{g/ml}$ ) had no effect on PPF and significantly increased the mean miniature IPSC amplitude, indicating a postsynaptic mechanism of action. Acute LPS pre-treatment potentiated ethanol (44 mM) effects on eIPSPs in WT mice and restored ethanol's augmenting effects on the eIPSP amplitude in CD14 knockout (CD14 KO) mice. Both the LPS and ethanol (44-66 mM) augmentation of eIPSPs was diminished significantly in most CeA neurons of CD14 KO mice; however, ethanol at the highest concentration tested (100 mM) still increased eIPSP amplitudes. By contrast, ethanol pre-treatment occluded LPS augmentation of eIPSPs in WT mice and had no significant effect in CD14 KO mice. Furthermore, (+)-naloxone, a TLR4-MD-2 complex inhibitor, blocked LPS effects on eIPSPs in WT mice and delayed the ethanol-induced potentiation of GABAergic transmission. In CeA neurons of CD14 KO mice, (+)-naloxone alone diminished eIPSPs, and subsequent co-application of 100 mM ethanol restored the eIPSPs to baseline levels. In summary, these results indicate that TLR4 and CD14 signaling play an important role in the acute ethanol effects on GABAergic transmission in the CeA and support the idea that CD14 and TLR4 may be therapeutic targets for treatment of alcohol abuse.

### **Blockade of D3 Receptors by YQA14 Inhibits Cocaine's Rewarding Effects and Relapse to Drug-seeking Behavior in Rats**

Song R, Bi GH, Zhang HY, Yang RF, Gardner EL, Li J, Xi ZX.

*Neuropharmacology* 2014; 77: 398-405.

Preclinical studies suggest that dopamine D3 receptor (D3R) antagonists are promising for the treatment of drug abuse and addiction. However, few D3R antagonists have potential to be tested in humans due to short half-life, toxicity or limited preclinical research into pharmacotherapeutic efficacy. Here, the authors report on a novel D3R antagonist YQA14, which has improved half-life and pharmacokinetic profile and which displays potent pharmacotherapeutic efficacy in attenuating cocaine

reward and relapse to drug-seeking behavior. Electrical brain-stimulation reward (BSR) in laboratory animals is a highly sensitive experimental approach to evaluate a drug's rewarding effects. The authors found that cocaine (2 mg/kg) significantly enhanced electrical BSR in rats (i.e., decreased stimulation threshold for BSR), while YQA14 alone had no effect on BSR. Pretreatment with YQA14 significantly and dose-dependently attenuated cocaine-enhanced BSR. YQA14 also facilitated extinction from drug-seeking behavior in rats during early behavioral extinction, and attenuated cocaine- or contextual cue-induced relapse to drug-seeking behavior. YQA14 alone did not maintain self-administration in either naïve rats or in rats experienced at cocaine self-administration. YQA14 also inhibited expression of repeated cocaine-induced behavioral sensitization. These findings suggest that YQA14 may have pharmacotherapeutic potential in attenuating cocaine-taking and cocaine-seeking behavior. Thus, YQA14 deserves further investigation as a promising agent for treatment of cocaine addiction.

**A Novel mGluR5 Antagonist, MFZ 10-7, Inhibits Cocaine-taking and Cocaine-seeking Behavior in Rats** Keck TM, Zou MF, Bi GH, Zhang HY, Wang XF, Yang HJ, Srivastava R, Gardner EL, Xi ZX, Newman AH. *Addiction Biology* 2014; 19: 195-209.

Pre-clinical studies suggest that negative allosteric modulators (NAMs) of the metabotropic glutamate receptor subtype 5 (mGluR5), including 2-methyl-6-(phenylethynyl)pyridine (MPEP), 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) and fenobam are highly effective in attenuating drug-taking and drug-seeking behaviors. However, both MPEP and MTEP have no translational potential for use in humans because of their off-target effects and short half-lives. Here, the authors report that 3-fluoro-5-[(6-methylpyridin-2-yl)ethynyl]benzonitrile (MFZ 10-7), a novel mGluR5 NAM, is more potent and selective than MPEP, MTEP and fenobam in both in vitro binding and functional assays. Similar to MTEP, intraperitoneal administration of MFZ 10-7 inhibited intravenous cocaine self-administration, cocaine-induced reinstatement of drug-seeking behavior and cocaine-associated cue-induced cocaine-seeking behavior in rats. Although MFZ 10-7 and MTEP lowered the rate of oral sucrose self-administration, they did not alter total sucrose intake. Further, MFZ 10-7 appeared to be more potent than MTEP in inducing downward shifts in the cocaine dose-response curve, but less effective than MTEP in attenuating sucrose-induced reinstatement of sucrose-seeking behavior. MFZ 10-7 and MTEP had no effect on basal locomotor behavior. These findings not only provide additional evidence supporting an important role for mGluR5 in cocaine reward and addiction, but also introduce a new tool for both in vitro and in vivo investigations with which to further characterize this role.

#### **Patent Applications Filed**

Kunos G, Iyer MR, Resat C, Rice KC. Novel Peripherally Restricted **CB1 Receptor Inverse Agonists for the Treatment of Diabetes and Obesity**. U.S. Provisional Patent Application filed November 13, 2012. Cannabinoid Receptor Mediating Compounds. U.S. Patent application filed November 12, 2013 as PCT/US2013/069686.

Alving CR, Matyas GR, Mayorov A, Rice KC, Iyer MR, Cheng K, Li F, Jacobson AE. **Induction Of Highly Specific Antibodies To A Hapten But Not To A Carrier Peptide By Immunization With An Adjuvanted Hapten-Peptide Conjugate Associated With Liposomes**. U. S. Provisional Patent Application, filed 08 February 2012. U.S. Patent application PCT/US13/25350 filed 08 February 2013.



## **Integrative Neuroscience Research Branch**

### **Structural Biology Section**

#### **How Adenylate Cyclase Choreographs the Pas de Deux of the Receptors' Heteromerization**

**Dance** Woods AS and Jackson SN. How adenylate cyclase choreographs the pas de deux of the Receptors heteromerization dance. Neuroscience 2013; 238: 335-344.

The authors' work suggests that heteromer formation mainly involves linear motifs (LMs) found in disordered regions of proteins. Local disorder imparts plasticity to LMs. Most molecular recognition of proteins occurs between short linear segments known as LMs. Interaction of short continuous epitopes is not constrained by sequence and has the advantage of resulting in interactions with micromolar affinities which suit transient, reversible complexes such as receptor heteromers. Electrostatic interactions between epitopes of the G-protein coupled receptors (GPCR) involved are the key step in driving heteromer formation forward. The first step in heteromerization involves phosphorylating Ser/Thr in an epitope containing a casein kinase 1/2-consensus site. These data suggest that dopaminergic neurotransmission, through cAMP-dependent protein kinase A (PKA), slows down heteromerization. The negative charge, acquired by the phosphorylation of a Ser/Thr in a PKA consensus site in the Arg-rich epitope, affects the activity of the receptors involved in heteromerization by causing allosteric conformational changes, due to the repulsive effect generated by the negatively charged phosphate. In addition to modulating heteromerization, it affects the stability of the heteromers' interactions and their binding affinity. So here is have an instance where phosphorylation is not just an on/off switch; instead by weakening the noncovalent bond, heteromerization acts like a rheostat that controls the stability of the heteromer through activation or inhibition of adenylate cyclase by the neurotransmitter dopamine, depending on which dopamine receptor it docks at.

#### **MALDI/Post Ionization-Ion Mobility Mass Spectrometry of Noncovalent Complexes of**

**Dopamine Receptors' Epitopes** Woods AS, Jackson SN, Lewis EK, Egan T, Muller L, Tabet JC, Schultz JA. J Proteome Res. 2013; 12: 1668-1677.

Protein domains involved in receptor heteromer formation are disordered and rich in the amino acids necessary for the formation of noncovalent complexes (NCX). The authors present mass spectral NCX data from proteins and protein receptors' epitopes obtained by combining ion mobility (IM) and MALDI. They focus on NCX involved in heteromer formation occurring between epitopes of the Dopamine D2 (D2R) and Adenosine A2A receptors (A2AR) as well as D2R and the  $\alpha 2$  nicotinic (NR) receptor subunit. The IM data yield information on the gas phase conformation of the singly charged NCX that are observed either directly from MALDI or as codesorbed neutrals that are subsequently postionized by a time-delayed excimer laser pulse directed onto a portion of the neutral plume created by the MALDI desorption laser. Imaging mass spectrometry of the matrix/epitope dried droplet surface shows that the acidic and basic epitopes and their NCX are found to be spatially collocated within regions as small as  $25 \times 50 \mu\text{m}^2$ . Subtle differences in the relative abundance of protonated and cationized NCX and epitopes are measured in spatial regions near the sodium-rich outer border of the droplet.

#### **Gangliosides and Ceramides Change in a Mouse Model of Blast Induced Traumatic Brain Injury**

Woods AS et al. ACS Neuroscience 2013; 4: 594-600.

Explosive detonations generate atmospheric pressure changes that produce nonpenetrating blast-induced "mild" traumatic brain injury (bTBI). The structural basis for mild bTBI has been extremely controversial. The present study applies matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging to track the distribution of gangliosides in mouse brain tissue that were exposed

to very low levels of explosive detonations (2.5–5.5 psi peak overpressure). The authors observed major increases of the ganglioside GM2 in the hippocampus, thalamus, and hypothalamus after a single blast exposure. Moreover, these changes were accompanied by depletion of ceramides. No neurological or brain structural signs of injury could be inferred using standard light microscopic techniques. The first source of variability is generated by the latency between blast and tissue sampling (peak intensity of the blast wave). These findings suggest that subtle molecular changes in intracellular membranes and plasmalemma compartments may be biomarkers for biological responses to mild bTBI. This is also the first report of a GM2 increase in the brains of mature mice from a nongenetic etiology.

**A New Interpretative Paradigm for Conformational Protein Diseases** Agnati LF, Guidolin D, Ciruela F, Carone C, Vallelunga A, Escuela DO, Woods AS, Genedani S, Fuxe K. *Curr Protein Pept Sci.* 2013; 14: 141-160.

Conformational Protein Diseases (CPDs) comprise over 40 clinically and pathologically diverse disorders in which specific altered proteins accumulate in cells or tissues of the body. The most studied are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, prion diseases, inclusion body myopathy, and the systemic amyloidoses. They are characterized by three dimensional conformational alterations, which are often rich in  $\beta$ - structure. Proteins in this non-native conformation are highly stable, resistant to degradation, and have an enhanced tendency to aggregate with like protein molecules. The misfolded proteins can impart their anomalous properties to soluble, monomeric proteins with the same amino acid sequence by a process that has been likened to seeded crystallization. However, these potentially pathogenic proteins also have important physiological actions, which have not completely characterized. This opens up the question of what process transforms physiological actions into pathological actions and most intriguing, is why potentially dangerous proteins have been maintained during evolution and are present from yeasts to humans. In the present paper, the authors introduce the concept of mis-exaptation and of mis-tinkering since they may help in clarifying some of the double edged sword aspects of these proteins. Against this background an original interpretative paradigm for CPDs will be given in the frame of the previously proposed Red Queen Theory of Aging.

## **Behavioral Neuroscience Section**

**Novel Effects of Dopamine in Memory Consolidation** Kramar CP, Chefer VI, Wise RA, Medina JH, Barbano MF. *Neuropsychopharmacology.* 2014 Jan 20. doi: 10.1038/npp.2014.11. [Epub ahead of print].

Cocaine is thought to be addictive because it elevates dopamine levels in the striatum, reinforcing drug-seeking habits. Cocaine also elevates dopamine levels in the hippocampus, a structure involved in contextual conditioning as well as in reward function. Hippocampal dopamine promotes the late phase of consolidation of an aversive step-down avoidance memory. Here, the authors examined the role of hippocampal dopamine function in the persistence of the conditioned increase in preference for a cocaine-associated compartment. Blocking dorsal hippocampal D1-type receptors (D1Rs) but not D2-type receptors (D2Rs) 12h after a single training trial extended persistence of the normally short-lived memory; conversely, a general and a specific phospholipase C-coupled D1R agonist (but not a D2R or adenylyl cyclase-coupled D1R agonist) decreased the persistence of the normally long-lived memory established by three-trial training. These effects of D1 agents were opposite to those previously established in a step-down avoidance task, and were here also found to be opposite to those in a lithium chloride-conditioned avoidance task. After returning to normal following cocaine injection,

dopamine levels in the dorsal hippocampus were found elevated again at the time when dopamine antagonists and agonists were effective: between 13 and 17h after cocaine injection. These findings confirm that, long after the making of a cocaine-place association, hippocampal activity modulates memory consolidation for that association via a dopamine-dependent mechanism. They suggest a dynamic role for dorsal hippocampal dopamine in this late-phase memory consolidation and, unexpectedly, differential roles for late consolidation of memories for places that induce approach or withdrawal because of a drug association.

**Lesions of Cholinergic PPTg Neurons Fail to Affect Cocaine or Heroin Reward** Steidl S, Wang H, Wise RA PLoS One. 2014 Jan 21; 9(1): e84412. doi: 10.1371/journal.pone.0084412. eCollection 2014 Jan 21.

Cholinergic input to the ventral tegmental area (VTA) is known to contribute to reward. Although it is known that the pedunculopontine tegmental nucleus (PPTg) provides an important source of excitatory input to the dopamine system, the specific role of PPTg cholinergic input to the VTA in cocaine reward has not been previously determined. The authors used a diphtheria toxin conjugated to urotensin-II (Dtx::UII), the endogenous ligand for urotensin-II receptors expressed by PPTg cholinergic but not glutamatergic or GABAergic cells, to lesion cholinergic PPTg neurons. Dtx::UII toxin infusion resulted in the loss of 95.78 ( $\pm 0.65$ )% of PPTg cholinergic cells but did not significantly alter either cocaine or heroin self-administration or the development of cocaine or heroin conditioned place preferences. Thus, cholinergic cells originating in PPTg do not appear to be critical for the rewarding effects of cocaine or of heroin.

**Integration of Proponent and Opponent Process Theories of Addiction** Wise RA, Koob GF. Neuropsychopharmacology 2014; 39: 254-262.

What is the defining property of addiction? The authors dust off a several-decades-long debate about the relative importance of two forms of reinforcement—positive reinforcement, subjectively linked to drug-induced euphoria, and negative reinforcement, subjectively linked to the alleviation of pain—both of which figure importantly in addiction theory; each of these forms has dominated addiction theory in its time. They agree that addiction begins with the formation of habits through positive reinforcement and that drug-opposite physiological responses often establish the conditions for negative reinforcement to come into play at a time when tolerance, in the form of increasing reward thresholds, appears to develop into positive reinforcement. Wise's work has tended to focus on positive-reinforcement mechanisms that are important for establishing drug-seeking habits and reinstating them quickly after periods of abstinence, whereas Koob's work has tended to focus on the negative-reinforcement mechanisms that become most obvious in the late stages of sustained addiction. While the authors tend to agree with each other about the early and late stages of addiction, they hold different views as to (i) the point between early and late at which the diagnosis of 'addiction' should be invoked, (ii) the relative importance of positive and negative reinforcement leading up to this transition, and (iii) the degree to which the specifics of negative reinforcement can be generalized across the range of addictive agents.

## **Behavioral Neuroscience Branch**

### **Neurocircuitry of Motivation Section**

#### **Similar Roles of Substantia Nigra and Ventral Tegmental Dopamine Neurons in Reward and Aversion**

Ilango A, Kesner AJ, Keller KL, Stuber GD, Bonci A, Ikemoto S. J Neurosci. 2014 Jan 15; 34(3): 817-822. doi: 10.1523/Journal of Neuroscience.1703-13.2014. Dopamine neurons in the ventral tegmental area (VTA) are implicated in affective functions. However, it is unclear to what extent dopamine neurons in substantia nigra pars compacta (SNc) play such roles. TH-Cre transgenic mice received adeno-associated viral vectors encoding channelrhodopsin2 (ChR2), halorhodopsin (NpHR), or control vector into the VTA or SNc, resulting in selective expression of these opsins in dopamine neurons. Mice with ChR2 learned instrumental responding to deliver photostimulation into the VTA or SNc and also sought for the compartment where they received photostimulation (i.e., operant place preference). Operant place preference scores were highly correlated with self-stimulation responses. In contrast, mice with NpHR avoided the compartment where they received photostimulation into the VTA, SNc, or dorsal striatum, whereas control mice did not. These observations suggest that the excitation and inhibition of SNc dopamine neurons elicit positive and negative affective effects, respectively, similar to those of VTA dopamine neurons.

### **Molecular Mechanisms of Behavior Unit**

**New Technologies for Studying Neuronal Ensembles in Addiction** Cruz FC, Koya E, Guez-Barber DH, Bossert JM, Lupica CR, Shaham Y, Hope BT. Nature Reviews Neuroscience (November 2013) 14:743-754. PMID: 24088811.

Correlational data suggest that learned associations are encoded within neuronal ensembles. However, it has been difficult to prove that neuronal ensembles mediate learned behaviours because traditional pharmacological and lesion methods, and even newer cell type-specific methods, affect both activated and non-activated neurons. In addition, previous studies on synaptic and molecular alterations induced by learning did not distinguish between behaviourally activated and non-activated neurons. Here, the authors describe three new approaches--Daun02 inactivation, FACS sorting of activated neurons and Fos-GFP transgenic rats--that have been used to selectively target and study activated neuronal ensembles in models of conditioned drug effects and relapse. They also describe two new tools--Fos-tTA transgenic mice and inactivation of CREB-overexpressing neurons--that have been used to study the role of neuronal ensembles in conditioned fear.

### **Neuroimaging Research Branch**

#### **A Preliminary Study Suggests that Nicotine and Prefrontal Dopamine Affect Cortico-striatal Areas in Smokers with Performance Feedback**

Lee MR, Gallen CL, Ross TR, Kurup P, Salmeron BJ, Hodgkinson CA, Goldman D, Stein EA, Enoch M-A. Genes Brain Behavior 2013; 12: 554-563. Nicotine and tonic dopamine (DA) levels [as inferred by catechol-O-methyl transferase (COMT) Val158Met genotype] interact to affect prefrontal processing. Prefrontal cortical areas are involved in response to performance feedback, which is impaired in smokers. The authors investigated whether there is a nicotine×COMT genotype interaction in brain circuitry during performance feedback of a reward task. They scanned 23 healthy smokers (10 Val/Val homozygotes, 13 Met allele carriers) during two fMRI sessions while subjects were wearing a nicotine or placebo patch. A significant

nicotine×COMT genotype interaction for BOLD signal during performance feedback in cortico-striatal areas was seen. Activation in these areas during the nicotine patch condition was greater in Val/Val homozygotes and reduced in Met allele carriers. During negative performance feedback, the change in activation in error detection areas such as anterior cingulate cortex (ACC)/superior frontal gyrus on nicotine compared to placebo was greater in Val/Val homozygotes compared to Met allele carriers. With transdermal nicotine administration, Val/Val homozygotes showed greater activation with performance feedback in the dorsal striatum, area associated with habitual responding. In response to negative feedback, Val/Val homozygotes had greater activation in error detection areas, including the ACC, suggesting increased sensitivity to loss with nicotine exposure. Although these results are preliminary due to small sample size, they suggest a possible neurobiological mechanism underlying the clinical observation that Val/Val homozygotes, presumably with elevated COMT activity compared to Met allele carriers and therefore reduced prefrontal DA levels, have poorer outcomes with nicotine replacement therapy.

### **Greater Externalizing Personality Traits Predict Less Error-related Insula and Anterior Cingulate Cortex Activity in Acutely Abstinent Smokers**

Carroll, AJ, Sutherland, MT, Salmeron BJ, Ross TJ, Stein EA. *Addiction Biology*, 2013 Dec 13. doi: 10.1111/adb.12118. [Epub ahead of print].

Attenuated activity in performance-monitoring brain regions following erroneous actions may contribute to the repetition of maladaptive behaviors such as continued drug use. Externalizing is a broad personality construct characterized by deficient impulse control, vulnerability to addiction and reduced neurobiological indices of error processing. The insula and dorsal anterior cingulate cortex (dACC) are regions critically linked with error processing as well as the perpetuation of cigarette smoking. As such, the authors examined the interrelations between externalizing tendencies, erroneous task performance, and error-related insula and dACC activity in overnight-deprived smokers (n=24) and non-smokers (n=20). Participants completed a self-report measure assessing externalizing tendencies (Externalizing Spectrum Inventory) and a speeded Flanker task during functional magnetic resonance imaging scanning. The authors observed that higher externalizing tendencies correlated with the occurrence of more performance errors among smokers but not non-smokers. Suggesting a neurobiological contribution to such suboptimal performance among smokers, higher externalizing also predicted less recruitment of the right insula and dACC following error commission. Critically, this error-related activity fully mediated the relationship between externalizing traits and error rates. That is, higher externalizing scores predicted less error-related right insula and dACC activity and, in turn, less error-related activity predicted more errors. Relating such regional activity with a clinically relevant construct, less error-related right insula and dACC responses correlated with higher tobacco craving during abstinence. Given that inadequate error-related neuronal responses may contribute to continued drug use despite negative consequences, these results suggest that externalizing tendencies and/or compromised error processing among subsets of smokers may be relevant factors for smoking cessation success.

### **Gender Differences in Neural-behavioral Response to Self-observation During a Novel fMRI Social Stress Task**

Lee MR, Cacic K, Demers C, Haroon M, Heishman S, Hommer D, Epstein D, Ross TJ, Stein EA, Heilig M, Salmeron BJ. *Neuropsychologia* 2014; 53: 257-263.

The neural correlates of response to psychosocial stress and gender differences therein are difficult to model experimentally as this type of stressor is difficult to induce in a brain imaging environment. The Trier Social Stress Test (TSST), a behavioral paradigm that reliably induces moderate levels of stress was thus modified for the MRI environment. To determine the neurobehavioral basis of gender differences in response to observing oneself under social evaluative stress, 26 subjects (14 females)

performed the TSST while being videotaped. During fMRI scanning, subjects were shown alternating video clips of two SELF or a same-sex OTHER performing the TSST. Subjects rated their stress level immediately after the video clips. GENDER differences in the [SELF-OTHER] contrast were analyzed. There was a GENDER×CONDITION interaction such that only women reported increased subjective stress during video feedback of their TSST session. A whole brain analysis (SELF vs. OTHER) showed activation in the bilateral insula, inferior, middle and superior frontal gyri. Greater recruitment was seen among males in some of these same areas in the context of significantly lower stress ratings. Activation of areas involved in inhibitory control and sensory awareness might contribute to the significantly lower stress ratings in males. Understanding these gender differences is relevant to disorders of stress and self-concept.

**Large Scale Brain Network Coupling Predicts Acute Nicotine Abstinence Effects on Craving and Cognitive Function** Lerman C, Gu H, Yang Y, Ruparel K, Stein, EA. JAMA Psychiatry 2014 Mar 12. doi: 10.1001/jamapsychiatry.2013.4091. [Epub ahead of print].

Interactions of large-scale brain networks may underlie cognitive dysfunctions in psychiatric and addictive disorders. To test the hypothesis that the strength of coupling among 3 large-scale brain networks—salience, executive control, and default mode—will reflect the state of nicotine withdrawal (vs smoking satiety) and will predict abstinence-induced craving and cognitive deficits and to develop a resource allocation index (RAI) that reflects the combined strength of interactions among the 3 large-scale networks. A within-subject functional magnetic resonance imaging study in an academic medical center compared resting-state functional connectivity coherence strength after 24 hours of abstinence and after smoking satiety. The authors examined the relationship of abstinence-induced changes in the RAI with alterations in subjective, behavioral, and neural functions. They included 37 healthy smoking volunteers, aged 19 to 61 years, for analyses. The main outcome measures were inter-network connectivity strength (primary) and the relationship with subjective, behavioral, and neural measures of nicotine withdrawal during abstinence vs smoking satiety states (secondary). The RAI was significantly lower in the abstinent compared with the smoking satiety states (left RAI,  $P = .002$ ; right RAI,  $P = .04$ ), suggesting weaker inhibition between the default mode and salience networks. Weaker inter-network connectivity (reduced RAI) predicted abstinence-induced cravings to smoke ( $r = -0.59$ ;  $P = .007$ ) and less suppression of default mode activity during performance of a subsequent working memory task (ventromedial prefrontal cortex,  $r = -0.66$ ,  $P = .003$ ; posterior cingulate cortex,  $r = -0.65$ ,  $p = .001$ ). Alterations in coupling of the salience and default mode networks and the inability to disengage from the default mode network may be critical in cognitive/affective alterations that underlie nicotine dependence.

**Cocaine-dependence Alters Temporal Difference Error Prediction Signals for Non-drug**

**Rewards** Rose, EJ, Salmeron, BJ, Ross, TJ, Waltz, J, Schweitzer, J, McClure, SM and Stein, EA.

Cocaine-dependence alters temporal difference error prediction signals for non-drug rewards.

Neuropsychopharmacology 2014 Jan 29. doi: 10.1038/npp.2014.21. [Epub ahead of print].

Cocaine dependence impacts drug-related, dopamine-dependent reward processing, yet its influence on non-drug reward processing is unclear. Here, the authors investigated cocaine-mediated effects on reward learning using a natural food reinforcer. Cocaine-dependent subjects ( $N=14$ ) and healthy controls ( $N=14$ ) learned to associate a visual cue with a juice reward. In subsequent functional imaging sessions they were exposed to trials where juice was received as learned, withheld (negative temporal difference error (NTDE)), or received unexpectedly (positive temporal difference error (PTDE)). Subjects were scanned twice in sessions that were identical, except that cocaine-dependent participants received cocaine or saline 10min before task onset. In the insula, precentral and postcentral gyri NTDE signals were greater, and PTDE-related function was reduced in cocaine-dependent subjects.

Compared with healthy controls, in the cocaine-dependent group PTDE signals were also reduced in medial frontal gyrus and reward-related function, irrespective of predictability, was reduced in the putamen. Group differences in error-related activity were predicted by the time as last self-administered cocaine use, but TDE function was not influenced by acute cocaine. Thus, cocaine dependence seems to engender increased responsiveness to unexpected negative outcomes and reduced sensitivity to positive events in dopaminergic reward regions. Although it remains to be established if these effects are a consequence of or antecedent to cocaine dependence, they likely have implications for the high-cocaine use recidivism rates by contributing to the drive to consume cocaine, perhaps via influence on dopamine-related reward computations. The fact that these effects do not acquiesce to acute cocaine administration might factor in binge-related escalated consumption.

### **Cortico-amygdala Coupling as a Marker of Early Relapse Risk in Cocaine Addicted Individuals**

McHugh MJ, Demers CH, Salmeron BJ, Devous MD, Stein EA, Adinoff B. *Frontiers in Psychiatry Addictive Disorders and Behavioral Dyscontrol* 5:16. doi: 10.3389/fpsyt.2014.00016, 2014. Addiction to cocaine is a chronic condition characterized by high rates of early relapse. This study builds on efforts to identify neural markers of relapse risk by studying resting-state functional connectivity (rsFC) in neural circuits arising from the amygdala, a brain region implicated in relapse-related processes including craving and reactivity to stress following acute and protracted withdrawal from cocaine. Whole-brain resting-state functional magnetic resonance imaging connectivity (6min) was assessed in 45 cocaine-addicted individuals and 22 healthy controls. Cocaine-addicted individuals completed scans in the final week of a residential treatment episode. To approximate preclinical models of relapse-related circuitry, separate seeds were derived for the left and right basolateral (BLA) and corticomedial (CMA) amygdala. Participants also completed the Iowa Gambling Task, Wisconsin Card Sorting Test, Cocaine Craving Questionnaire, Obsessive-Compulsive Cocaine Use Scale and Personality Inventory. Relapse within the first 30days post-treatment (n=24) was associated with reduced rsFC between the left CMA and ventromedial prefrontal cortex/rostral anterior cingulate cortex (vmPFC/rACC) relative to cocaine-addicted individuals who remained abstinent (non-relapse, n=21). Non-relapse participants evidenced reduced rsFC between the bilateral BLA and visual processing regions (lingual gyrus/cuneus) compared to controls and relapsed participants. Early relapse was associated with fewer years of education but unrelated to trait reactivity to stress, neurocognitive and clinical characteristics or cocaine use history. Findings suggest that rsFC within neural circuits implicated in preclinical models of relapse may provide a promising marker of relapse risk in cocaine-addicted individuals. Future efforts to replicate the current findings and alter connectivity within these circuits may yield novel interventions and improve treatment outcomes.

### **Dorsal and Ventral MPFC Circuitry in Rodent Models of Cocaine Use: Relevance to Novel Therapies for Human Drug Addiction** Jasinska AJ, Chen W, Bonci A, Stein EA, *Addiction Biology*, 2014 Mar 13. doi: 10.1111/adb.12132. [Epub ahead of print].

Although the importance of the medial prefrontal cortex (MPFC) in cocaine addiction is well established, its precise contribution to cocaine seeking, taking and relapse remains incompletely understood. In particular, across two different models of cocaine self-administration, pharmacological or optogenetic activation of the dorsal MPFC has been reported to sometimes promote and sometimes inhibit cocaine seeking. The authors highlight important methodological differences between the two experimental paradigms and propose a framework to potentially reconcile the apparent discrepancy. They also draw parallels between these pre-clinical models of cocaine self-administration and human neuro-imaging studies in cocaine users, and argue that both lines of evidence point to dynamic interactions between cue-reactivity processes and control processes within the dorsal MPFC circuitry. From a translational perspective, these findings underscore the importance of interventions and

therapeutics targeting not just a brain region, but a specific computational process within that brain region, and may have implications for the design and implementation of more effective treatments for human cocaine addiction.

## **Cellular Neurobiology Research Branch**

### **Behavioral Neurophysiology Research Section**

**Orbitofrontal Cortex as a Cognitive Map of Task Space** Wilson RC, Takahashi YK, Schoenbaum G, Niv. Y. Neuron 2013,81:267-279. oi: 10.1016/j.neuron.2013.11.005.

Orbitofrontal cortex (OFC) has long been known to play an important role in decision making. However, the exact nature of that role has remained elusive. Here, the authors propose a unifying theory of OFC function. The authors hypothesize that OFC provides an abstraction of currently available information in the form of a labeling of the current task state, which is used for reinforcement learning (RL) elsewhere in the brain. This function is especially critical when task states include unobservable information, for instance, from working memory. The authors use this framework to explain classic findings in reversal learning, delayed alternation, extinction, and devaluation as well as more recent findings showing the effect of OFC lesions on the firing of dopaminergic neurons in ventral tegmental area (VTA) in rodents performing an RL task. In addition, they generate a number of testable experimental predictions that can distinguish their theory from other accounts of OFC function.



## **EXTRAMURAL POLICY AND REVIEW ACTIVITIES**

### **Receipt, Referral, and Review**

- Total # of grant applications: 1,329
- DA primary: 877
- Institute-based reviews (Sixteen Grants and fourteen Contracts reviews)

### **Grant Reviews**

1. PA-11-197 (K99/R00): NIH Pathway to Independence Award (K99/R00)
2. PAR-10-220 (P30): NIDA Core Center of Excellence Grant Program (P30)
3. PAR-13-222 (P50): NIDA Research "Center of Excellence" Grant Program (P50)
4. RFA-DA-14-008 (DP1): FY14 NIDA Avant-Garde Award Program for HIV/AIDS Research
5. PA13-302: Multi-site clinical Trials
6. RFA-DA-14-013 (R43/R44): Abuse-Resistant and Abuse-Deterrent Formulations and Devices to Avoid the Abuse, Misuse and Diversion of Prescription Opioids by Patients (SBIR)
7. PA13-302 Revision (U01): Original RFA-DA10-018: Medications Development for Substance Related Disorders (R01)
8. RFA-DA-14-010 (R01): HIV/AIDS and Substance Use among Black/African American Women and Young MSM
9. PAR-12-086 (R21): Cutting-Edge Basic Research Awards (CEBRA) (R21)
10. PAR-12-066 (R03): NIDA I/START Small Grant Review
11. RFA-DA-14-012 (R21): Comorbid HIV, Chronic Pain, and Substance Use among Older Adults (R21)
12. RFA-DA-14-009 (R01): HIV/AIDS and Substance Use Among the Homeless and Unstably Housed (R01)
13. RFA-DA-14-011 (R01): Integrating Substance Abuse Prevention and Treatment within HIV/AIDS Service Delivery Settings
14. PA12-212 (R13): R13 Conference Grant Review (PA12-212)
15. RFA DA14-015 (U01): National Institute on Drug Abuse National Early Warning System (NEWS) Coordinating Center (U01)
16. PAR-13-222 (P50): SEP: NIDA Research "Center of Excellence" Grant Program (P50)

### **Contract Reviews**

1. N01DA-14-7789: NIDA Center for Genetic Studies (7789)
2. N43DA-14-5578 (Topic 151): Web Resource System for Prescription Drug Providers, Researchers and Users: The Prescription Drug Abuse Policy System (PDAPS) (5578; Phase I- Topic 151)
3. N43DA-14-5577 (Topic 152): Technological Tools to Facilitate Implementation of Evidence - Based Substance Abuse Prevention Interventions among the Military (557; Phase I- Topic 152)
4. N43DA-14-2239 (Topic 153): Products to Prevent (Lethal) Drug-induced Respiratory Depression (2239; Phase I- Topic 153)
5. N43DA-14-1208 (Topic 154): Bundled Service for Designing Methodologically Rigorous Animal Studies (1208; Phase I- Topic 154)
6. N43DA-14-5679 (Topic 155): Affordable Care Act (ACA) Web Platform to Integrate Behavioral Health & Prevention with Primary Care (5679; Phase I- Topic 155)

7. N01DA-14-5576: National Addiction and HIV Data Archive Program (NAHDAP) (5576)
8. N01DA-14-8916: Non-Clinical ADME Studies (8916)
9. N01DA-14-2237: Data, Statistics, and Clinical Trial Support (2237)
10. N01DA-14-1152: NIDAMED: Outreach and Education to Health Care Providers on Substance Use (1152)
11. N01DA-14-8917: Medication Discovery/Rat Models/Relapse/Cocaine Self Administration (8917)
12. N44DA-14-2233: SBIR Phase II Topic 147; mHealth (Opiod) (2233)
13. N44DA-14-2235: SBIR Phase II Topic 147; Smoking Application (2235)
14. N44DA-14-2236: SBIR Phase II Topic 147; mSmart Modile App (2236)
15. N44DA-14-2238: SBIR Phase II MedCheck - Medication Adherence System (2238)
16. N44DA-14-4418: SBIR Phase II An in situ Opiod Drug Deactivation Kit for Home Use (4418)
17. N44DA-14-4421: SBIR Phase II At-Home Deactivation (4421)

### **Certificates of Confidentiality**

Between December 5, 2013 and March 5, 2014 NIDA OEA processed 117 Certificate of Confidentiality applications.

### **Staff Training and Development**

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued to provide open forums for discussions and presentations.

Dr. Jose Ruiz delivered a presentation entitled, “Overview of the NIH Peer Review Process and Electronic Submission” to participants of the February 10-11, 2014 National Institute on Drug Abuse Office of Diversity and Health Disparities Research Development Seminar Series Part I Workshop.

### **Other Review Activities**

The CTN Data and Safety Monitoring Board met April 9, 2014, to discuss progress of protocol CTN 0054, Accelerated Development of Additive Pharmacotherapy Treatment (ADAPT).

**CONGRESSIONAL AFFAIRS SECTION**  
**(Prepared April 25, 2014)**

**APPROPRIATIONS**

The President's budget request for NIDA for FY 2015 is \$1.023 billion. This compares to a 2014 "enacted" level of \$1.016 billion. For NIH, the President requested \$30.362 billion, a 0.7% increase over the 2014 level.

**CONGRESSIONAL HEARINGS/MEETINGS**

**Past**

On February 25, 2014, NIDA Director Dr. Nora Volkow met with Congressman William Foster (D-IL) at his request. He is especially concerned about the rise of opiate abuse and addiction in his district.

On March 20, 2014, NIDA Deputy Director Dr. Wilson Compton participated in a staff briefing sponsored by the Senate Caucus for International Narcotics Control. The topic: opiate abuse and addiction. Other federal agencies participated, including ONDCP, SAMHSA, FDA, and DEA.

On April 2, 2014, NIDA Director Dr. Nora Volkow testified in front of the House Appropriations Committee, Subcommittee on Commerce, Science, Justice and Related Agencies. This was the budget hearing for the Drug Enforcement Administration. Subcommittee Chairman Frank Wolf (R-VA) invited Dr. Volkow to testify on the science of addiction, what we know and understand about addiction as a brain disease. With the current popular interest in marijuana and opiates issues, Chairman Wolf asked Dr. Volkow to focus some attention on those specific topics. He was extremely appreciative of her testimony, evidenced by a letter he sent to the President recommending to him that he meet with Dr. Volkow on these issues.

On April 22, 2014, NIH Director Dr. Francis Collins and NIDA Director Dr. Nora Volkow delivered keynote addresses to the third annual National Rx Drug Abuse Summit. Dr. Collins and Dr. Volkow were both personally invited by House Appropriations Chairman Harold Rogers (R-KY) to be part of this event. This was the first year Dr. Collins participated; Dr. Volkow has been a keynote speaker for each of the three years.

On April 23, 2014, NIDA Deputy Director Wilson Compton participated in a briefing sponsored by the Senate Committee on Health, Education, Labor and Pensions. Topic: Prescription Drug Abuse. At the request of the Committee, Dr. Compton focused on NIDA's role in addressing this issue. Other participating agencies included CDC and SAMHSA.

On April 24, 2014, NIDA Deputy Director Dr. Wilson Compton participated in a congressional briefing focused on the intersection of hepatitis C and opioid abuse, especially in young people. This briefing was organized by the Harm Reduction Coalition and the National Alliance of State & Territorial AIDS Directors.

On April 29, 2014, the Senate Appropriations Committee held a hearing on Driving Innovation Through Federal Investments. NIH Director Dr. Francis Collins testified.

On April 29, 2014, the House Energy and Commerce Subcommittee on Oversight and Investigations held a hearing on heroin and prescription drug abuse. NIDA Director Dr. Nora Volkow testified, along with other witnesses from SAMHSA and CDC.

On April 29, 2014, Senators Sheldon Whitehouse (D-RI) and Rob Portman (D-OH) sponsored the first in a series of Capitol Hill addiction forums. The first one is titled Addiction Forum: Overview of Addiction in the Criminal Justice System. Dr. Redonna Chandler, Acting Director, Division of Epidemiology, Services and Prevention Research, NIDA, presented as part of the opening panel. Dr. Chandler is a recognized national expert on this topic, having spent years working with DOJ and others to disseminate evidenced-based research.

On April 30, 2014, the Senate Veterans Affairs Committee held a hearing on overmedication, and the particular role of opioids in this discussion. Dr. Josephine Briggs, Director, NCCAM, testified along with representatives from the Department of Veterans Affairs and the Army.

### **Future expected events**

On May 9, 2014, at the request of the Congressional Hepatitis Caucus, NIDA Deputy Director Dr. Wilson Compton will participate in a briefing entitled Hepatitis on the Hill. Also invited to participate are HRSA and the Office of the Assistant Secretary for Health.

On May 14, 2014, the Senate Caucus on International Narcotics control will hold a hearing on the Causal Role Prescription Drug Abuse has had on the Increased Use of Heroin in the United States. Dr. Nora Volkow, Director, NIDA, will testify. Other expected witnesses include: Michael Botticelli, Acting Director, Office of National Drug Control Policy; Dr. H. Westley Clark, Director, Substance Abuse and Mental Health Services Administration; and Dr. Andrew Kolodny, Chief Medical Officer, Phoenix House.

On June 19, 2014, the House Oversight and Government Reform Subcommittee on Government Operations will hold a hearing on marijuana. Dr. Nora Volkow, Director, NIDA, will testify. This is the third in a series of hearings held by this Subcommittee on this topic. Also scheduled to testify is Dr. Douglas Throckmorton of FDA.

### **SOME BILLS OF INTEREST**

**HR 486** – On February 4, 2013, Representative William Keating (D-MA) introduced the Stop Tampering of Prescription Pills act of 2013, to amend the Food, Drug and Cosmetic Act to incentivize the development of abuse-deterrent drugs. The bill was referred to the Committee on Energy and Commerce.

**HR 498** – On February 5, 2013, Representative Lucille Roybal-Allard (D-CA) introduced a bill to reauthorize the Sober Truth on Preventing Underage Drinking (STOP) Act. Representatives Rosa DeLauro (D-CT), and Frank Wolf (R-VA) were the only two original co-sponsors of the legislation. The bill was referred to the House Committee on Energy and Commerce.

**HR 499** – On February 5, 2013, Representative Jared Polis (D-CO) introduced the Ending Federal Marijuana Prohibition Act of 2013, to generally decriminalize and change the way the Controlled Substances Act is applied to marijuana. The bill was referred to the Committee on the Judiciary, the Committee on Ways and Means, the Committee on Energy and Commerce, the Committee on Natural Resources, and the Committee on Agriculture.

**HR 672** -- On February 13, 2013, Representative Nick Rahall (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Energy and Commerce and the Committee on the Judiciary. See also S 348.

**HR 1263** – On March 19, 2013, Representative Doris Matsui (D-CA) introduced the Excellence in Mental Health Act, to increase access to community behavioral health services for all Americans and to improve Medicaid reimbursement for community behavioral health services. The bill was referred to the Committee on Energy and Commerce. See also S 264, S 265.

**HR 1285** – On March 20, 2013, Representative Vern Buchanan (R-FL) introduced Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary, and Judiciary. See also S 621. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

**HR 1366** – On March 21, 2013, Representative Stephen Lynch (D-MA) introduced the Stop Oxycontin Abuse Act of 2013, to direct the Commissioner of Food and Drugs to modify the approval of any drug containing controlled-release oxycodone hydrochloride to limit such approval to use for the relief of severe-only instead of moderate-to-severe pain, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

**HR 1523** – On April 12, 2013, Representative Dana Rohrabacher (R-CA) introduced the Respect State Marijuana Laws Act of 2013, to amend the Controlled Substances Act to provide for a new rule regarding the application of the Act to marijuana, and for other purposes. The bill was referred to the Committee on the Judiciary and the Committee on Energy and Commerce.

**HR 3717** – On December 12, 2013, Representative Tim Murphy (R-PA) introduced the Helping Families in Mental Health Crisis Act of 2013, to make available needed psychiatric, psychological, and supportive services for individuals diagnosed with mental illness and families in mental health crisis, and for other purposes. The bill was referred to the House Committees on: Energy and Commerce; Judiciary; Energy and the Workforce; Ways and Means; and Science, Space and Technology.

**HR 4046** – On February 11, 2014, Representative Steven Cohen (D-TN) introduced the Unmuzzle the Drug Czar Act, to strike provisions that prohibit the Director of the Office of National Drug Control Policy from studying the legalization of marijuana, that require the Director to oppose any attempt to legalize marijuana, and for other purposes. The bill was referred to the Committees on Oversight and Government Reform, Judiciary, and Energy and Commerce.

**HR 4169** – On March 4, 2014, Donna Edwards (D-MD) introduced the Stop Overdose Stat (S.O.S.) Act, to prevent deaths occurring from drug overdoses. The bill would create a new CDC grant program focused on overdose prevention; create a new CDC grant program to improve fatal and nonfatal drug overdose surveillance and reporting capabilities; create a national task force that would develop a plan to reduce drug overdose deaths (NIDA explicitly included in this); and focus on overdose prevention research at NIDA (the bill authorizes \$5 million dollars a year for the next few years to do this work). The bill was referred to the Committee on Energy and Commerce, Subcommittee on Health.

**HR 4241** – On March 13, 2014, Representative Stephen Lynch (D-MA) introduced the Act to Ban Zohydro, to withdraw approval for the drug Zohydro ER and prohibit the Food and Drug Administration from approving such drug unless it is reformulated to prevent abuse. The bill was referred to the Committee on Energy and Commerce. See S. 213443024

**S 237** – On February 7, 2013, Senator Lisa Murkowski (R-AK) introduced the Advancing FASD Research, Prevention and Services Act, to amend the Public Health Service Act to reauthorize and extend the FAS prevention and services program, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

**S 264** – On February 7, 2013, Senator Debbie Stabenow (D-MI) introduced the Excellence in Mental Health Act, to expand access to community mental health centers and improve the quality of mental health care for all Americans. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See also S 265, HR 1263

**NOTE:** On March 31, 2014, Congress passed the Protecting Access to Medicare Act (H.R. 4302), which included a demonstration program based on the Excellence in Mental Health Act. The Excellence Act will increase Americans' access to community mental health and substance use treatment services while improving Medicaid reimbursement for these services.

**S 265** – On February 7, 2013 Senator Jack Reed (D-RI) introduced Community-Based Mental Health Infrastructure Improvements Act, to amend the Public Health Service Act to provide grants for community-based mental health infrastructure improvement. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also S 264, HR 1263

**S 348** – On February 14, 2013, Senator John Rockefeller (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also HR 672.

**S 621** – On March 20, 2013, Senator Joe Manchin (D-WV) introduced the Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary. See also HR 1285. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

**S 644** – On March 21, 2013, Senator Robert Casey (D-PA) introduced the Preventing Abuse of Cough Treatments Act of 2013, to amend the Food, Drug, and Cosmetic Act to prevent the abuse of dextromethorphan, and for other purposes. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

**S 1277** – On July 10, 2013, Senator Barbara Boxer (D-CA) introduced the Combating Prescription Drug Abuse Act, to establish a commission for the purpose of coordinating efforts to reduce prescription drug abuse, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

**S 2134** -- On March 13, 2014, Senator Joe Manchin (D-WV) introduced the Act to Ban Zohydro, to withdraw approval for the drug Zohydro ER and prohibit the Food and Drug Administration from approving such drug unless it is reformulated to prevent abuse. The bill was referred to the Committee on Health, Education, Labor and Pensions. See HR 4241.

## INTERNATIONAL ACTIVITIES

### **Binational Agreements**

#### ***NIDA Signs Binational Agreements with Peru and the United Arab Emirates***

NIDA has signed binational agreements with the Peruvian Instituto Nacional de Salud and the United Arab Emirates (UAE) National Rehabilitation Center (NRC). NIDA Director Nora D. Volkow, M.D. and Instituto Nacional de Salud Chief Cesar Augusto Cabezas Sánchez, M.D., signed the Peruvian binational agreement in January 2014. The agreement focuses on scientific and academic exchange among established scientists and postdoctoral researchers, sharing research methods and tools, holding joint workshops, and collaborative activities between the Instituto Nacional de Salud and the NIDA Clinical Trials Network.

Dr. Volkow and NRC Director General His Excellency Hamad Al Ghafri, M.B.B.S., M.P.H., Ph.D., signed the UAE agreement February 26, 2014, at NIDA headquarters. The two institutions agreed to cooperate on research and methods for epidemiology, prevention, addiction pharmacotherapy drug discovery, and phase 1 and 2 clinical trials; NIDA international fellowships, research training exchanges, and medical education programs; and joint scientific workshops.

The signing was part of visit to NIDA by a delegation from the NRC. The delegation attended a NIDA Division of Epidemiology, Prevention and Services Research (DESPR) seminar where Rob Orwin, Ph.D., Westat, discussed evaluation of the Substance Abuse and Mental Health Services Administration (SAMHSA) Strategic Prevention Framework State Incentive Grant program. Following the DESPR seminar NRC and NIDA staff met for discussions and presentations. NRC Surveillance Section Head Naseeba Al Ozaibi, Ph.D. and Eve Reider, Ph.D., DESPR, led the discussion of prevention activities. NRC Senior Public Health Education Specialist Amna Al Marzouqi, Ph.D., and Moira O'Brien, M.Phil., DESPR, reviewed epidemiology and surveillance programs in the two countries. Lori Ducharme, Ph.D., DESPR, discussed NIDA treatment services research. Stephanie Older, OSPC, described public education and information programs, including NIDA's Drug Facts Week and Chat Day. IP Director Steven W. Gust, Ph.D., described the institute's research training fellowships and mechanisms for scientific exchanges.

### **Research Results**

#### ***WHO Releases Guidelines on Managing Substance Use During Pregnancy***

The World Health Organization has released the first evidence-based global guidelines to prevent and treat substance use by pregnant women. The plain-language recommendations also can be used to help pregnant women and their family members make healthy decisions about alcohol, tobacco, and illicit drug use. Designed for use in both low- and high-resource countries, the document identifies principles and best practices in six areas:

1. Screening and brief intervention
2. Psychosocial interventions
3. Detoxification
4. Dependence management
5. Infant feeding
6. Management of infant withdrawal.

The guidelines evolved from a 2009 NIDA International Program meeting, *Treating Addiction During Pregnancy: Exploring Multinational Perspectives to Build a Treatment Approach Consensus*. Invitees



completed a premeeting survey that attracted enthusiastic responses from researchers in 22 different countries on six continents. Participants identified experts and stakeholders to develop a draft consensus statement and asked WHO to consider developing the guidelines.

In mid-2012, the WHO departments of Mental Health and Substance Abuse and the Tobacco Free Initiative began coordinating the guideline development process, which was funded by the U.S. and Norwegian governments. NIDA and the National Institute of Alcohol Abuse and Alcoholism provided additional support for evidence reviews and planning meetings.

Former NIDA INVEST Fellow Guilherme Borges, Sc.D., Instituto Nacional de Psiquiatria Ramon de la Fuente Muñiz, Mexico, co-chaired the guideline development group, and NIDA Distinguished International Scientist Irma Kirtadze, M.D., Alternative Georgia Addiction Research Center, Republic of Georgia, served as an external peer reviewer. NIDA grantee Hendrée Jones, Ph.D., University of North Carolina at Chapel Hill, who chaired the 2009 NIDA meeting, also served on the WHO guidelines development group. Dr. Jones led the NIDA-funded Maternal Opioid Treatment: Human Experimental Research (MOTHER) study that found buprenorphine maintenance treatment safe for opioid-dependent pregnant women and their babies. IP Director Steven W. Gust, Ph.D., DCNBR Behavioral & Brain Development Branch Chief Cheryl Anne Boyce, Ph.D., and Women and Sex/Gender Differences Research Program Deputy Coordinator Samia Dawud Noursi, Ph.D., participated in the guideline development group meetings. Download the WHO *Guidelines for the management of substance use and substance use disorders in pregnancy* here: [http://www.who.int/substance\\_abuse/activities/pregnancy\\_substance\\_use/en/](http://www.who.int/substance_abuse/activities/pregnancy_substance_use/en/).

### ***Ukrainian Study Concludes Methadone Maintenance Treatment Acceptability and Outcomes Do Not Depend on IDUs' HIV Status***

Former INVEST/CTN and NIDA Hubert H. Humphrey Drug Abuse Research Fellow Sergii Dvoriak, M.D., Ph.D., Ukrainian Institute of Public Health Policy, is the lead author on an article reporting that methadone maintenance treatment (MMT) was well accepted and effective in reducing drug use and HIV risk behaviors among opioid-dependent HIV+ and HIV- individuals in Kiev. It is the first study of MMT acceptability and outcome as a function of HIV status among Ukrainian injecting drug users. Dr. Dvoriak and George E. Woody, Ph.D., University of Pennsylvania led the NIDA-supported research team through an R21 grant (DA021073). The study, Methadone maintenance for HIV positive and HIV negative patients in Kyiv: Acceptability and treatment response, was published in *Drug and Alcohol Dependence*, 137:62-67; doi: 10.1016/j.drugalcdep.2014.01.008.

### **Meetings**

#### ***WHO Begins Developing Guidelines on Managing Opioid Overdose***

IP Director Steven W. Gust, Ph.D., was among the international drug abuse experts who met to discuss drafting World Health Organization (WHO) evidence-based guidelines for managing opioid overdose. The meeting was held February 19-20, 2014, in Geneva. According to WHO, between 70,000 and 100,000 people die annually from overdose, and opioid-related respiratory depression causes many of those deaths. The guidelines development group examined evidence from clinical trials evaluating the effectiveness, risks, and benefits of various opioid overdose interventions and discussed best practices established in different countries. Participants also discussed legal and ethical issues emerging from adoption of take-home naloxone doses to ensure that people dependent on opioids, their families, peers, and first responders have access to this proven overdose treatment medication in cases of emergency. Advocates suggested that improving access to naloxone might reduce opioid overdose

deaths and provide treatment options in countries with limited access to health service for people who inject drugs.

### ***CTN International Forum Features Collaboration Reports***

International scientists presented their research during an international workshop at the Clinical Trials Network (CTN) Steering Committee Meeting, March 12, 2014, in Bethesda, Maryland. Greta Zaneti, M.S., University of Pavia, Italy, discussed her work examining clinical, research, and public health models to address problem gambling in order to begin designing a cognitive behavioral gambling intervention in collaboration with the Italian Department for Anti-drug Policies. Nathalie Gendron, Ph.D., assistant director of the Institute of Neurosciences, Mental Health and Addiction at the Canadian Institutes of Health Research, discussed the new Canadian Research Initiative in Substance Misuse, which uses the CTN model to create teams of university researchers and community-based treatment providers. Fabian Fiestas, Ph.D., Centro Nacional de Salud Pública at the Instituto Nacional de Salud de Peru, reviewed current conditions and suggested future directions for substance abuse treatment in Peru following the recently signed binational agreement between NIDA and Instituto Nacional de Salud de Peru. Clinical Trials Unit Coordinator Rodrigo Marin Navarrete, Ph.D., Instituto Nacional de Psiquiatria Ramón de la Fuente of Mexico, presented results from a multi-site randomized clinical trial that assessed motivational enhancement treatment in outpatient addiction care centers in Mexico.

### ***Symposium Examines Mental Health and Substance Abuse in Africa***

Researchers from Africa, Europe, the Middle East, and the United States gathered in Jimma, Ethiopia, February 17-19, 2014, for a symposium to build research capacity on addiction and mental health. Fikre Lemessa, Ph.D., president of Jimma University chaired the conference. NIDA grantee Mustafa al'Absi, Ph.D., chaired the scientific committee. Dr. al'Absi directs the Khat Research Program and the Duluth Medical Research Institute at the University of Minnesota Duluth. The International Brain Research Organization Africa Regional Committee and the bi-annual Africa and Middle East Conference on Addiction provided financial and logistical support for the symposium. The Khat Research Program plans to organize similar symposia in other African and Middle Eastern countries. See the program for the Jimma-Minnesota symposium at <http://www.khatresearch.org/JIMIS>.

### **Fellowships**

#### ***Postdoctoral Drug Abuse Research Program for U.S. and French Scientists***

The application deadline was May 1 for the 2014 round of postdoctoral research exchange fellowships cosponsored by NIDA and Institut National de la Santé et de la Recherche Médicale (Inserm). In fiscal year 2014, NIDA will support up to two awards for French scientists to work in the United States with an eligible NIDA grantee, and Inserm will support up to two awards for U.S. scientists to work in France with an eligible mentor at an Inserm research unit or center. U.S. mentors should be a current NIDA-funded extramural or intramural researcher conducting research in computational neuroscience, bioinformatics, statistics, genetics, or epigenetics related to addiction. French mentors must be conducting research in computational neuroscience, bioinformatics, statistics, genetics, epigenetics, neurobiology, or clinical trials in drug abuse and addiction. Read about the fellowships and the research interests of the eligible mentors here: <http://www.drugabuse.gov/international/nida-inserm-postdoctoral-drug-abuse-research-fellowships-us-french-scientists>.

#### ***NIDA Names Georgian Researcher as Distinguished International Scientist***

Irma Kirtadze, M.D., senior researcher at Alternative Georgia Addiction Research Center in the Republic of Georgia, has received a NIDA Distinguished International Scientist Collaboration Award

(DISCA). Dr. Kirtadze will use the award to work with her U.S. partner, Hendrée Jones, Ph.D., University of North Carolina at Chapel Hill. The two are developing a manual to implement supported employment programs for women with substance use disorders. During Dr. Kirtadze's DISCA exchange visit, the two will interview vocational services providers in North Carolina and conduct qualitative analysis of the responses. Once she returns to the Republic of Georgia, Dr. Kirtadze will interview vocational services providers and women participating in the NIDA-supported binational research project, HIV and Drug Use in Georgian Women (R01 DA029880), for which she and Dr. Jones serve as principal investigators. The research partners will use the qualitative analyses of the interviews to develop the manual and plan to seek funding for implementation and evaluation of the manual once it is complete. Learn more about the DISCA program here:

<http://www.drugabuse.gov/international/distinguished-international-scientist-collaboration-program>.

### **CTN INVEST Fellows**

Since 2008, NIDA's International Program and the Clinical Trials Network (CTN) have jointly offered fellowships to non-U.S. scientists. Each INVEST fellow works with a CTN mentor affiliated with one of the 13 CTN Nodes. Fellows may conduct their research in any aspect of the CTN research agenda on drug abuse and addiction, such as intervention research, clinical trials methodology, or drug abuse treatment, as well as HIV/AIDS prevention. On March 12, 2014, the CTN held an International Forum that included a presentation from the current CTN INVEST fellow as well as presentations from representatives from Canada, Peru and Mexico.

### **Other International Activities**

Dr. Ivan Montoya, DPMCD, was invited to give a plenary lecture at the 41<sup>st</sup> annual conference of the Spanish Society of Alcohol and Addictions (Socidrogalcohol) in Seville, Spain on April 5<sup>th</sup>, 2014.

Dr. Ivan Montoya, DPMCD, received the *Honorary Member Award* by the Spanish Society of Alcohol and Addictions (Socidrogalcohol) in Seville, Spain on April 5<sup>th</sup>, 2014, for his contributions to expanding drug abuse research in Spain.

Dr. Bruce Hope, IRP, was invited to present a talk entitled "Neuronal ensembles in addiction" at a panel session at the European Winter Conference on Brain Research in Brides les Bains, France on March 19, 2014.

Dr. Marilyn Huestis was an invited keynote speaker at the International Association of Law and Forensic Science congress in Dubai, United Arab Emirates from March 31<sup>st</sup> to April 3<sup>rd</sup>. Dr. Huestis presented "Designer Drugs, the Emerging Face of Drug Abuse." Dr. Huestis also presented two lectures at the National Rehabilitation Center of Abu Dhabi, United Arab Emirates on "Residual Cannabinoids in Blood, Brain Neuroadaptation and Extended Psychomotor Impairment during Sustained Abstinence in Chronic Frequent Cannabis Smokers," and "In Utero Drug Exposure and Adverse Child Development" on March 29<sup>th</sup>-31<sup>st</sup>, 2014.

Dr. Amina Woods spoke at the Commissariat à l'Energie Atomique et aux Energies Alternatives, Saclay France Seminar on February 13, 2014 on "What nano-particles implantation brings to tissue imaging".

Dr. Geoffrey Schoenbaum, IRP, gave invited lectures at the ENS group in Paris, and OIST in Okinawa and Tamagawa University in Tokyo.

## **PROGRAM ACTIVITIES/FOAs**

### **New NIDA RFAs**

On April 4, 2014, NIDA issued an RFA entitled **Avenir Award Program for Research on Substance Abuse and HIV/AIDS (DP2)** [\*\*RFA-DA-15-007\*\*](#). Avenir means future in French, and this award looks toward the future by supporting early stage investigators proposing highly innovative studies. The award will support those in an early stage of their career who may lack the preliminary data required for an R01 grant, but who propose high impact research and who show promise of being tomorrow's leaders in the field. NIDA has developed two Avenir Award Programs, one for HIV/AIDS research and the other for genetics or epigenetics studies. The Avenir Award Program for Research on Substance Abuse and HIV/AIDS will support creative individuals who wish to pursue innovative research at the nexus of substance abuse and HIV/AIDS. The Avenir Award Program for Research on Substance Abuse and HIV/AIDS will support research approaches for substance using populations with or at risk for HIV/AIDS that may lead to improved preventive interventions, improved therapies and/or long term retention in care, and ultimately, eradication of HIV. Open date: October 12, 2014. Application due date(s): November 12, 2014, November 12, 2015, November 14, 2016, by 5:00 PM local time of applicant organization. AIDS application due date(s): November 12, 2014, November 12, 2015, November 14, 2016, by 5:00 PM local time of applicant organization.

On March 27, 2014, NIDA issued an RFA entitled **Avenir Award Program for Genetics or Epigenetics of Substance Abuse (DP2)** [\*\*RFA-DA-15-006\*\*](#). Avenir means future in French, and this award looks toward the future by supporting early stage investigators proposing highly innovative studies. The award will support those in an early stage of their career who may lack the preliminary data required for an R01 grant, but who propose high impact research and who show promise of being tomorrow's leaders in the field. NIDA has developed two Avenir Award Programs, one for HIV/AIDS research and the other for genetics or epigenetics studies. The Genetic Avenir Award program supports early stage investigators proposing highly innovative studies that open new areas of research for the genetics or epigenetics of addiction. The award will support those in an early stage of their career who may lack the preliminary data required for an R01 grant, but who propose high impact research and who show promise of being tomorrow's leaders in the field of genetics or epigenetics of substance abuse. Open date: July 18, 2014. Application due date(s): August 18, 2014, August 18, 2015, August 18, 2016, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On February 13, 2014, NIDA issued an RFA entitled **NIDA Avant-Garde Award Program for HIV/AIDS and Drug Use Research (DP1)** [\*\*RFA-DA-15-004\*\*](#). The NIDA Avant-Garde Award Program for HIV/AIDS Research supports individual scientists of exceptional creativity who propose high-impact research that will open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among drug abusers. The term "avant-garde" is used to describe highly innovative approaches that have the potential to be transformative. The proposed research should reflect approaches and ideas that are substantially different from those already being pursued by the investigator or others. The NIDA Avant-Garde award supports innovative, basic research that may lead to improved preventive interventions or therapies; creative, new strategies to prevent disease transmission; novel approaches to improve disease outcomes; and creative approaches to eradicating HIV or improving the lives of those living with HIV. Open date: June 29, 2014.

Application due date(s): July 29, 2014, July 29, 2015, July 29, 2016, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On February 5, 2014, NIDA issued an RFA entitled **Advancing Exceptional Research on HIV/AIDS and Substance Abuse (R01)** [RFA-DA-15-005](#). This FOA will support highly innovative R01 applications on HIV/AIDS and drug abuse and will complement the Avant-Garde Award Program for HIV/AIDS research. The [Avant-Garde award](#) supports individuals who conduct high-risk, high-reward research and does not require a detailed research plan. Applications submitted under this FOA are expected to have a detailed research plan and preliminary data. This FOA focuses on innovative research projects that have the potential to open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among substance abusers. The nexus with substance abuse should be clearly described. This FOA is open to both individual researchers and research teams and is not limited to any one area of research on HIV and substance use. Open date: June 30, 2014. Application due date(s): July 31, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On January 31, 2014, NIDA issued an RFA entitled **Medications Development Centers of Excellence Cooperative Program (U54)** [RFA-DA-15-003](#). This FOA solicits Specialized Center Cooperative Agreement (U54) applications to provide support for Medications Development Centers of Excellence (MDCE) with emphasis solely on clinical research directed towards the identification, evaluation, and development of safe and effective medications and biologics for treatment of substance use disorders (SUDs). Research may focus on both currently approved or novel investigational products. Centers may have a translational project to reinforce rationale of medications for testing. Any preclinical work proposed must be specifically devoted to the reinforcement of rationale of medications planned for clinical testing during the life of the project. Open date: n/a. Application due date(s): April 25, 2014. AIDS application due date(s): Not Applicable.

### **New NIDA Program Announcements**

On March 26, 2014, NIDA issued PAs entitled **Effects of Cannabis Use and Cannabinoids on the Developing Brain (R21)** [PA-14-162](#), **(R01)** [PA-14-163](#), **(R03)** [PA-14-164](#). This Funding Opportunity Announcement (FOA) encourages applications from institutions and organizations that propose to study the effects and functional consequences of cannabis and cannabinoid exposures on the developing brain, from pre-, peri-, post-natal development through young adulthood in animal models and humans. Topics of interest pertaining to this PA include, but are not limited to: molecular and cellular mechanisms of cannabis/cannabinoid effects on the developing brain; long term functional consequences of cannabis/cannabinoid exposure on learning and memory, cognitive and emotional development. Open date: May 5, 2014 (R01), May 16, 2014 (R21 and R03). Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On March 3, 2014, NIDA, in collaboration with NIDDK, issued PAs entitled **Prevention and Treatment of Substance Using Populations with or at Risk for HCV (R34)** [PA-14-135](#), **(R21)** [PA-14-136](#), **(R01)** [PA-14-137](#). This Funding Opportunity Announcement outlines priority areas for high impact clinical and basic research for at-risk substance using populations, including those infected with or at risk for HIV. In particular, this FOA encourages research focused on prevention and treatment of Hepatitis C Virus (HCV) to reduce new infections and identify and treat existing



infections more effectively. This FOA is informed by priority areas in the 2011 HHS Action Plan, Combating the Silent Epidemic of Viral Hepatitis: Action Plan for the Prevention, Care and Treatment of Viral Hepatitis. Open date: May 5, 2014 (R01), May 16, 2014 (R21 and R34). Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On February 20, 2014, NIDA issued PAs entitled **Synthetic Psychoactive Drugs and Strategic Approaches to Counteract Their Deleterious Effects (R03) [PAR-14-104](#), (R21) [PAR-14-105](#), (R01) [PAR-14-106](#)**. The purpose of this Funding Opportunity Announcement (FOA) is to support research to deepen our knowledge of the use of synthetic psychoactive drugs, their mechanisms of action, their health effects, and development of prevention strategies and strategies to treat patients in emergency departments and long range treatment. Open date: May 5, 2014 (R01), May 16, 2014 (R03 and R21). Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On February 4, 2014, NIDA issued PAs entitled **Neuroimmune Signaling and Function in Substance Use Disorders (R01) [PA-14-084](#), (R21) [PA-14-083](#)**. The purpose of this Funding Opportunity Announcement (FOA) is to encourage the submission of research project grant applications that propose to examine the molecular, cellular, circuit, and behavioral responses to neuroimmune signaling within the central nervous system (CNS) as it pertains to the initiation, escalation, and maintenance of, and the neurological consequences resulting from, substance use disorders (SUDs), and to abstinence and withdrawal from, and subsequent relapse of, drug use. The goal of this understudied area of research is to determine the extent to which neuroimmune responses contribute to or protect against current and future risk and consequences of SUDs. Open date(s): May 5, 2014 (R01), May 16, 2014 (R21). Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

### **New FOAs Issued by the NIH Roadmap**

On April 18, 2014, the NIH Common Fund issued a Roadmap RFA entitled **Undiagnosed Diseases Gene Function Research (R21) [RFA-RM-14-005](#)**. The purpose of this Exploratory/Developmental Research Funding Opportunity is to support gene function studies in collaboration with the Undiagnosed Diseases Network (UDN) building upon the NIH Intramural Research Program's Undiagnosed Diseases Program (NIH-UDP). Responsive applications will propose to investigate the underlying genetics, biochemistry and/or pathophysiology of newly diagnosed diseases in association with the respective gene variant(s) identified through the UDN. In recent years, gene function studies combined with genetic and genomic analyses and metabolic studies have greatly improved diagnoses of these very rare diseases and advanced scientific knowledge of the underlying pathogenesis. This initiative is funded through the NIH Common Fund, which supports cross-cutting programs that are expected to have exceptionally high impact. Open date: May 23, 2014. Application due date(s): June 23, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On February 12, 2014, the NIH Common Fund issued a Roadmap RFA entitled **Limited Competition: Renewal Applications for Technology Development for New Affinity Reagents Against the Human Proteome (U01)** [RFA-RM-14-002](#). The purpose of the NIH Common Fund Protein Capture Reagents Program (PCRP) aims to develop over time the capacity to generate a community resource of high quality renewable affinity reagents for all human proteins (see <https://commonfund.nih.gov/proteincapture/>). This Funding Opportunity Announcement (FOA) is a component of the PCRP, and it seeks renewal applications to cooperative agreements that were funded through [RFA-RM-10-018](#). Novel approaches for producing validated protein affinity reagents have been developed by the presently funded technology centers and have demonstrated potential for substantially reducing cost and increasing throughput. To determine if any of these approaches can be used in a large-scale proteome project, applicants funded through this FOA are expected to demonstrate scalability by generating affinity reagents recognizing at least three hundred human protein targets. Open date: May 25, 2014. Application due date(s): April 25, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

**New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant**

**Development of Software and Analysis Methods for Biomedical Big Data in Targeted Areas of High Need (U01)** [RFA-HG-14-020](#)

**New PAs Issued by Other NIH/HHS Components in which NIDA is a participant**

**Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science (R01)** [PA-14-155](#)

**Extended Development, Hardening and Dissemination of Technologies in Biomedical Computing, Informatics and Big Data Science (R01)** [PA-14-156](#)

**Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science (R41/R42)** [PA-14-157](#)

**Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science (R43/R44)** [PA-14-154](#)

**Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship (Parent F31)** [PA-14-147](#)

**Ruth L. Kirschstein National Research Service Award Individual Predoctoral Fellowship to Promote Diversity in Health-Related Research (Parent F31 - Diversity)** [PA-14-148](#)

**Ruth L. Kirschstein National Research Service Award (NRSA) Individual Postdoctoral Fellowship (Parent F32)** [PA-14-149](#)

**Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral MD/PhD or Other Dual-Doctoral Degree Fellowship (Parent F30)** [PA-14-150](#)

**Behavioral Interventions to Address Multiple Chronic Health Conditions in Primary Care (R01) [PA-14-114](#)**

**Eradication of HIV-1 from Central Nervous System Reservoirs (R01) [PA-14-095](#)**

**HIV Infection of the Central Nervous System (R01) [PA-14-094](#)**

**Bioengineering Research Partnerships (BRP) R01 [PAR-14-092](#)**

**Direct Phase II SBIR Grants to Support Biomedical Technology Development [PAR-14-088](#)**

**Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp) [PA-14-077](#)**

**Successor-in-Interest (Type 6 Parent) [PA-14-079](#)**

**Change of Grantee Organization (Type 7 Parent) [PA-14-078](#)**

#### **New RFAs Issued by the NIH Blueprint for Neuroscience Research**

**NIH Blueprint Program for Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences (R25) [RFA-NS-14-010](#)**

#### **New NIDA Administrative Supplement Program Announcements**

On February 26, 2014, NIDA issued an administrative supplement PAR entitled **Additional Research Training Positions for NIDA-Supported NRSA Institutional Training (T32) Grants (Admin Supp) [PAR-14-115](#)**. The purpose of this administrative supplement program is to provide funds to support additional training positions on current NIDA-supported institutional Ruth L. Kirschstein National Research Service Award (NRSA) programs to enhance research training capacity in NIDA mission-critical areas. Mission-critical areas include, but are not limited to, genetics and epigenetics, computational neuroscience, HIV/AIDS, medications development, marijuana/ cannabinoid and tobacco/nicotine and health care reform/delivery innovations. Duration of supplement support is one to two years, depending on the number of years remaining on the parent T32 grant. Applications were due March 21, 2014 by 5:00 PM local time of applicant organization. Earliest start dates for awards is July 1, 2014.

On March 5, 2014, NIDA, in collaboration with NIAAA and NCI, issued an administrative supplement PA entitled **Additional Research Training Positions for NIAAA-, NIDA-, NCI-supported NRSA Institutional Training (T32) Grants (Admin Supp) [PA-14-116](#)**. The purpose of this administrative supplement program is to provide funds to support additional training positions on NIAAA-, NIDA-, or NCI-supported T32 programs to help meet the goals of Collaborative Research on Addiction at NIH (CRAN). Duration of support is up to three years, depending on the number of years remaining on the parent T32 grant. Applications were due by April 9, 2014, by 5:00 PM local time of applicant organization. Earliest start date is July 1, 2014.



NIDA will be awarding 20 travel awards to NIDA-supported NRSA trainees, NRSA fellows, and Minority Supplement recipients to attend the [2014 CPDD Meeting](#). The application deadline for these awards was December 19, 2013.

## **OTHER PROGRAM ACTIVITIES**

### **CTN UPDATE**

A total of 54 protocols have been initiated since 2001, including multi-site clinical trials (38), multi-site surveys (3), studies in special populations (8), and secondary analyses of data across various trials (5). In addition, 28 ancillary studies have been supported by CTN and non-CTN funds. Over 16,000 participants have been enrolled in CTN studies. Information on protocols can be found at:

<http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies>

### **NIDA's Blending Initiative**

Accelerating the dissemination of research-based drug abuse treatment into clinical practice is a priority for the National Institute on Drug Abuse (NIDA) and represents the core mission of the [Blending Initiative](http://www.drugabuse.gov/blending-initiative) (<http://www.drugabuse.gov/blending-initiative>). Through the Blending Initiative, NIDA partners with professional organizations and other institutions dedicated to the training and education of junior fellows/residents to support the development of expertise in substance use disorders (SUDs) within medical and clinical settings. These training awards aim: 1) to promote knowledge of evidence-based SUD treatment within medical specialties, 2) to advance medical care for patients with substance use disorders, and 3) to facilitate the academic growth, advanced education, and development of future researchers and clinicians in SUDs and medicine and thereby invest in the future of the field.

The training awardees from two partnerships (the Emergency Medicine Foundation and the American Academy of Child and Adolescent Psychiatry) were introduced to the CTN Steering Committee at the March 11-13, 2014 meeting.

Two additional training award partnerships have been initiated with the Society for the Teachers of Family Medicine and the Society for Adolescent Health and Medicine.

## COMMUNICATIONS

### PUBLICATIONS/VIDEOS

#### NIDA Publications and Online Resources

“Heads Up” (Scholastic/NIDA) *Drugs + Your Body: It Isn’t Pretty!* interactive poster (January 2014): <http://www.scholastic.com/drugs-and-your-body/>

“Research Report Series: Hallucinogens and Dissociative Drugs” (Revised January 2014)  
<http://www.drugabuse.gov/publications/research-reports/hallucinogens-dissociative-drugs>

“Research Report Series: Heroin” (Revised February 2014):  
<http://www.drugabuse.gov/publications/research-reports/heroin>

“Marijuana: Facts Parents Need to Know” (Revised March 2014):  
<http://www.drugabuse.gov/publications/marijuana-facts-parents-need-to-know>

#### **NIDA Notes**

Nineteen new articles and 2 videos (Elizabeth Howell and Joni Rutter, also available as podcasts) have been posted on the *NIDA Notes* homepage. The *NIDA Notes* website has added an RSS feature whereby readers can subscribe to have new articles delivered directly to their browser or email. Three email blasts have been sent to subscribers -- two content updates and one announcing RSS feeds. December - February article views numbered 103,000 which are up, partly as a result of a Google AdWords campaign.

#### **Videos**

- **What's New at NIDA:**  
**Office of Science Policy and Communication Director's notes for January**  
<http://youtu.be/jw0eUbvJRyo>
- **NDFW Teen MOTS, Part III**  
[http://youtu.be/Y\\_gf4Wpe5xA](http://youtu.be/Y_gf4Wpe5xA)
- **NDFW Dance Party 2014**  
<http://youtu.be/olPg12Cgec4>
- **IQ Challenge Videos**  
<http://youtu.be/LXixFul6wFk>
- **Three (3) NDFW Dance Party Tweets (Images and Videos)**  
<http://www.flickr.com/photos/nida-nih/12105064696> <http://www.flickr.com/photos/nida-nih/12104779564> <http://www.flickr.com/photos/nida-nih/12104687563>
- **CEWG-NIDA, Heroin in the Twin Cities**  
<http://www.youtube.com/watch?v=8DMIMa-uubI&list=UUfXHx9qyqeB3ezHQnHk8zXA>
- **NIDA Research Spotlight: "Sex, Drugs and Facebook"**  
<http://youtu.be/Lonhn1BElis>
- **NIDA TV Spotlight: Communities That Care**  
<http://youtu.be/nmMhCxo4u1w>

## **CTN-Related Publications**

Four editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 29 CTN studies are now available on the NIDA Data Sharing website <http://www.nida.nih.gov/CTN/Data.html>. Over 2,300 data sets have been downloaded by researchers from 55 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The CTN Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

## **Other Publications**

Boyce CA, Maholmes V, Spatz Widom CA Society for Research in Child Development (SRCD) Policy Report has been published as a product of the NIDA, NICHD and ACF May, 2012 joint meeting entitled “Neuroscience and Child Maltreatment Expert Panel Meeting.” Neuroscience and Child Maltreatment. SRCD Soc Policy Report. 2014 Apr; 27 (1).

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Fix BV, O'Connor RJ, Vogl LM, Smith DM, Bansal-Travers M, Conway KP, Ambrose B, Yang L, Hyland A. Patterns and Correlates of Polytobacco Use in the United States over a Decade: NSDUH 2002-2011. *Addictive Behaviors* 2014; 39: 768-781.

Ghitza, UE, Tai, B. Challenges and opportunities for integrating preventive substance-use-care services in primary care through the Affordable Care Act. *Journal of Health Care for the Poor and Underserved* 2014; 25(1 suppl): 36-45.

Glantz MD, Medina-Mora ME, Petukhova M, Andrade L H, Anthony JC, de Girolamo G, de Graaf R, Degenhardt L, Demyttenaere K, Florescu S, Gureje O, Haro J M, Horiguchi I, Karam EG, Kostyuchenko S, Lee S, Lépine J, Matschinger H, Neumark Y, Posada-Villa J, Sagar R, Stein DJ, Tomov T, Wells JE, Chatterji S, Kessler R, et al. Alcohol abuse in developed and developing countries in the World Mental Health Surveys: Socially defined consequences or psychiatric disorder? *American Journal on Addictions*. 2014; 23: 145–155.

Hiranita T, Kohut SJ, Soto PL, Tanda G, Kopajtic TA, Katz JL. Preclinical efficacy of N-substituted benzotropine analogs as antagonists of methamphetamine self-administration in rats. *Journal of Pharmacology and Experimental Therapeutics*, 348; 174–191: 2014.

Kirchner TR, Villanti AC, Cantrell J, Anesetti-Rothermel A, Ganz O, Conway KP, Vallone DM, Abrams DB. Tobacco retail outlet advertising practices and proximity to schools, parks and public

housing affect Synar underage sales violations in Washington D.C. Tobacco Control. Published Online First: February 25, 2014.

Pollock JD. Deep imaging technology needed for NIH BRAIN initiative. J Biomed Opt. 2014 Mar 1; 19(3): 30601. doi: 10.1117/1.JBO.19.3.030601.

Pollock JD, Wu DY, Satterlee JS. Molecular neuroanatomy: a generation of progress. Trends Neurosci. 2014 Feb; 37(2): 106-123. doi: 10.1016/j.tins.2013.11.001. Epub 2013 Dec 31.

Rich JD, Chandler RK, Brie WA, Dumont D, Wang E, Taxman FS, Allen SC, Clarke JG, Greifinger RB, Wildeman C, Osher FC, Rosenberg S, Haney C, Mauer M, Western B. How health care reform can transform the health of criminal justice-involved individuals. Health Affairs. 2014 Feb; 33(3).

Shirley MC, Sirocco KY Introduction to Special Section: ADHD, Impulsivity, and Alcohol Abuse. Exp Clinical Psychopharmacol. 2014 Apr; 22 (2) :97-99.

Valdiserri R, Khalsa J, Dan C, Holmberg S, Zibbell J, Holtzman D, Lubran R, Compton W. Confronting the Emerging Epidemic of HCV Infection Among Young Injection Drug Users. Am J Public Health. 2014 Mar 13. [Epub ahead of print].

In follow up to the joint NIAAA/NIDA workshop, “Building the Next Generation of Integrative Approaches for Understanding Comorbid Alcohol, Drug Abuse, and Attention Disorders” held last year on May 13-14, 2013; Karen Sirocco (NIDA) and Mariela Shirley (ORWH/OD/NIH) organized the “Special Section: ADHD, Impulsivity and Alcohol Abuse” in the April, 2014 edition of the journal Experimental and Clinical Psychopharmacology.

Drs. David Shurtleff, Cathrine Sasek, and Mary Kautz served as co-editors on a special NIDA 40<sup>th</sup> Anniversary Issue of Neuropharmacology, Volume 76 Part B, January 2014.

## **COMMUNITY AND PRESS EVENTS**

### **NIDA Director Dr. Nora Volkow Speaks at 2014 Clinton Foundation Health Matters Conference**

On January 14, 2014, in La Quinta, California, Dr. Nora Volkow participated in a panel discussion on prescription drug abuse and misuse at the Clinton Foundation Health Matters Conference. This conference served as the annual anchor event for the Clinton Health Matters Initiative which works to improve the health and well-being of people across the United States by activating individuals, communities, and organizations to make meaningful contributions to the health of others. The audience was comprised of approximately 450 senior business, healthcare, entertainment and community and sports leaders. The NIDA press office conducted social media outreach.

### **2014 Chat Day and National Drug Facts Week (NDFW)**

NIDA conducted its annual Chat Day (Jan 28) and NDFW (January 27 - February 2, 2014), which included over 1,000 events in 50 states. Approximately 100 high schools registered for Chat Day and close to 2,000 questions were answered by NIDA scientists. NIDA developed and distributed press and promotional materials, cultivated radio and organizational partnerships, pitched to select media, coordinated two Radio Media Tours for English and Spanish speaking audiences, participated in and filmed local events, and promoted the week via traditional and social media outreach.

### **NIDA Participates in Opening of *Target America Exhibit: Opening Eyes to the Damage Drugs Cause***

On February 11, 2014, NIDA's Redonna Chandler participated in the ribbon cutting ceremony for *Target America Exhibit: Opening Eyes to the Damage Drugs Cause*, an interactive traveling exhibit now housed at the Maryland Science Center that explores the effects of drugs on individuals and society. Dr. Chandler was joined by DEA Administrator Michele Leonhart, SAMSHA Special Assistant to the Director Richard Lucey, Mayor of Baltimore City Stephanie Rawlings-Blake, Special Assistant from the Office of Congressman Elijah Cummings Hope Williams, Chairman & CEO of the DEA Educational Foundation Bill Alden, and President & CEO of the Maryland Science Center Van Reiner. NIDA's Deputy Press Officer, Rachel Wolf, accompanied Dr. Chandler to provide press support during the event.

### **NIDA Joins ONDCP for Teleconference about Heroin and Opioid Abuse**

On February 11th, 2014, NIDA's Deputy Director Dr. Wilson Compton and Director of the Office of National Drug Control Policy Gil Kerlikowske held a media teleconference to discuss recent trends in opioid use in the United States, including heroin and prescription painkiller abuse. During the teleconference, they shared the latest data indicators regarding trends in opioid drug use and the actions currently underway to reduce drug use and its consequences. NIDA's Press Officer, Dr. Sheri Grabus, provided press support for Dr. Compton and promoted the teleconference via live tweets.

### **NIDA Director Meets with Washington Post Editorial Board**

On April 1, 2014, NIDA Director Dr. Nora Volkow met with the Washington Post Editorial Board in Washington, D.C. During the meeting, Washington Post Editorial Board members asked Dr. Volkow about the latest topics relevant to drug abuse research. These included the latest usage, trends, and research on marijuana, heroin, and prescription drug abuse, as well as other areas.

### **NIDA Director Testifies in front of House Appropriations Committee**

On April 2, 2014, NIDA Director Dr. Nora Volkow testified in front of the House Appropriations Committee, Subcommittee on Commerce, Science, Justice and Related Agencies during the budget hearing for the Drug Enforcement Administration. Subcommittee Chairman Frank Wolf (R-VA) invited Dr. Volkow to testify on the science of addiction, what we know and understand about addiction as a brain disease. With the current popular interest in marijuana and opiates issues, Chairman Wolf asked Dr. Volkow to focus some attention on those specific topics.

### **NIDA Deputy Director Participates in FDA Telebriefing about Naloxone Auto-Injector**

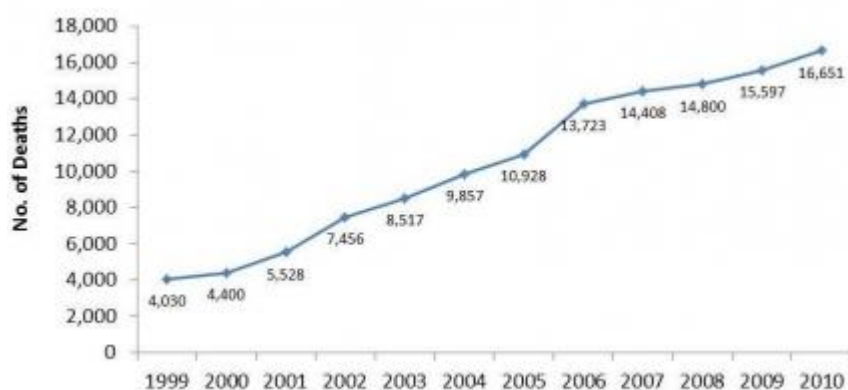
On April 3, 2014, NIDA Deputy Director Dr. Wilson Compton participated in an FDA multi-stakeholder telebriefing with other federal partners to highlight the approval of Evzio, a hand-held auto-injector naloxone prescription treatment that can be used by family members or caregivers to reverse opioid overdose.

## **PRESS RELEASE**

### **April 24, 2014: HHS leaders call for expanded use of medications to combat opioid overdose epidemic:**

*New England Journal of Medicine commentary describes that vital medications are currently underutilized in addiction treatment services and discusses ongoing efforts by major public health agencies to encourage their use*

A national response to the epidemic of prescription opioid overdose deaths was outlined yesterday in the New England Journal of Medicine by leaders of agencies in the U.S. Department of Health and Human Services. The commentary calls upon health care providers to expand their use of medications to treat opioid addiction and reduce overdose deaths, and describes a number of misperceptions that have limited access to these potentially life-saving medications. The commentary also discusses how medications can be used in combination with behavior therapies to help drug users recover and remain drug-free, and use of data-driven tracking to monitor program progress.



Number of prescription opioid related deaths 1999-2010

Source: [CDC WONDER](#)

The commentary was authored by leaders of the National Institute on Drug Abuse (NIDA) within the National Institutes of Health, the Centers for Disease Control and Prevention (CDC), the Substance Abuse and Mental Health Services Administration (SAMHSA), and the Centers for Medicare and Medicaid Services (CMS).

“When prescribed and monitored properly, medications such as methadone, buprenorphine, or naltrexone are safe and cost-effective components of opioid addiction treatment,” said lead author and

NIDA director Nora D. Volkow, M.D. “These medications can improve lives and reduce the risk of overdose, yet medication-assisted therapies are markedly underutilized.”

Research has led to several medications that can be used to help treat opioid addiction, including methadone, usually administered in clinics; buprenorphine, which can be given by [qualifying doctors](#); and naltrexone, now available in a once-a-month injectable, long-acting form. The authors stress the value of these medications and describe reasons why treatment services have been slow to utilize them. The reasons include inadequate provider education and misunderstandings about addiction medications by the public, health care providers, insurers, and patients. For example, one common, long-held misperception is that medication-assisted therapies merely replace one addiction for another – an attitude that is not backed by the science. The authors also discuss the importance of naloxone, a potentially life-saving medication that blocks the effects of opioids as a person first shows symptoms of an overdose.

The article describes how HHS agencies are collaborating with public and private stakeholders to expand access to and improve utilization of medication-assisted therapies, in tandem with other targeted approaches to reducing opioid overdoses. For example, NIDA is funding research to improve access to medication-assisted therapies, develop new medications for opioid addiction, and expand access to naloxone by exploring more user-friendly delivery systems (for example, nasal sprays). CDC is working with states to implement comprehensive strategies for overdose prevention that include medication-assisted therapies, as well as enhanced surveillance of prescriptions and clinical practices. CDC is also establishing statewide norms to provide better tools for the medical community in making prescription decisions.

“Prescription drug overdoses in the United States are skyrocketing. The good news is we can prevent this problem by stopping the source and treating the troubled,” said co-author and CDC director Tom Frieden, M.D., M.P.H. “It is critical that states use effective prescription drug tracking programs so we can improve prescribing practices and help get those who are abusing drugs into treatment.”

Charged with providing access to treatment programs, SAMHSA is encouraging medication-assisted therapy through the Substance Abuse Prevention and Treatment Block Grant as well as regulatory oversight of medications used to treat opioid addiction. SAMHSA has also developed an [Opioid Overdose Toolkit](#) to educate first responders in the use of naloxone to prevent overdose deaths. The toolkit includes easy-to-understand information about recognizing and responding appropriately to overdose, specific drug-use behaviors to avoid, and the role of naloxone in preventing fatal overdose.

“SAMHSA’s Opioid Overdose Toolkit is the first federal resource to provide safety and prevention information for those at risk for overdose and for their loved ones,” said co-author and SAMHSA Administrator Pamela S. Hyde, J.D. “It also gives local governments the information they need to develop policies and practices to help prevent and respond appropriately to opioid-related overdose.”

CMS is working to enhance access to medication-assisted therapies through a more comprehensive benefit design, as well as a more robust application of the Mental Health Parity and Addiction Equity Act.

“Appropriate access to medication-assisted therapies under Medicaid is a key piece of the strategy to address the rising rate of death from overdoses of prescription opioids,” said co-author Stephen Cha, M.D., M.H.S., chief medical officer for the Center for Medicaid and CHIP [Children’s Health Insurance Program] Services at CMS. “CMS is collaborating closely with partners across the country, inside and outside government, to improve care to address this widespread problem.”

However, the authors point out that success of these strategies requires engagement and participation of the medical community.

The growing availability of prescription opioids has increased risks for people undergoing treatment for pain and created an environment and marketplace of diversion, where people who are not seeking these medications for medical reasons abuse and sell the drugs because they can produce a high.



More than 16,000 people die every year in this country from prescription opioid overdoses, more than heroin and cocaine combined. According to [SAMHSA's 2012 National Survey on Drug Use and Health](#), almost 2.1 million people in the United States were dependent upon or abusing opioid pain relievers. More information on prescription opioid abuse can be found at: [www.drugabuse.gov/publications/research-reports/prescription-drugs](http://www.drugabuse.gov/publications/research-reports/prescription-drugs).

**Reference:** Medication-Assisted Therapies — Tackling the Opioid-Overdose Epidemic. Nora D. Volkow, M.D. (NIDA), Thomas R. Frieden, M.D., M.P.E. (CDC), Pamela S. Hyde, J.D. (SAMHSA), and Stephen Cha, M.D., M.H.S. (CMS). The New England Journal of Medicine, April 23, 2014: [www.nejm.org/doi/full/10.1056/NEJMp1402780](http://www.nejm.org/doi/full/10.1056/NEJMp1402780).

**April 25, 2014 -- NIDA announces new resources for healthcare providers.** NIDA introduced two new, science-based resources through its [NIDAMED](#) initiative to help healthcare professionals manage patients at risk for substance use disorders, including prescription drug abuse. The American College of Physicians (ACP) now houses an [Addressing Substance Use](#) online module that can be used to help with implementing screening, counseling, and referral to treatment. Also, the American Academy of Physician Assistants (AAPA) and the American Association of Nurse Practitioners (AANP) are now offering opioid and pain management courses. <http://www.drugabuse.gov/news-events/news>.

**April 18, 2014 -- Comprehensive prevention programs successful in decreasing HIV rates in people who inject drugs.** A new NIDA-funded large-scale study showed that comprehensive prevention programs can decrease HIV infection in injection drug users within the criminal justice system. This study analyzed the success of programs that included methadone maintenance therapy, syringe programs, health education, and antiretroviral therapy (in those affected with HIV – to reduce transmission of the disease). <http://www.drugabuse.gov/news-events/news-releases/2014/04/comprehensive-prevention-programs-successful-in-decreasing-hiv-rates-in-people-who-inject-drugs>

## **Science Spotlights and Announcements**

**February 4, 2014 - Medication may help patients with severe mental illness stay smoke-free.** Smokers with schizophrenia or bipolar disorders are three times more likely to abstain from smoking over the course of a year if they take varenicline. Although varenicline is an FDA-approved smoking cessation medication, it had not been proven effective for smokers with severe mental illness. The results of this study suggest that it is feasible to prescribe varenicline to these patients, which could lessen the health burdens caused by smoking in this population. <http://www.drugabuse.gov/news-events/news-releases/2014/02/medication-may-help-patients-severe-mental-illness-stay-smoke-free>

**February 26, 2014 - Transition services for drug using, HIV-infected inmates leaving jail should be gender-specific.** A NIDA-funded study shows that HIV-infected women who are released from jail are more likely to abuse cocaine, have co-occurring psychiatric disorders, and to have worse HIV treatment outcomes compared to men, underscoring the need for gender-specific interventions and services. <http://www.drugabuse.gov/news-events/news-releases/2014/02/transition-services-drug-using-hiv-infected-inmates-leaving-jail-should-be-gender-specific>



**February 27, 2014** - *NIDA's updated Heroin Research Report now available online.* Due to growing public concern about heroin and its potentially devastating effects, NIDA has updated its online Heroin Research Report. This Report offers the most current data on heroin use and its consequences as well as treatment options for heroin use disorders.

<http://www.drugabuse.gov/news-events/news-releases/2014/02/nidas-updated-heroin-research-report-now-available-online>

**March 27, 2014** - *Targeting delta opioid receptor may reduce pain without causing addiction.* NIDA funded a new study researching the delta opioid receptor (DOR), a pain receptor located under the skin that regulates minor skin sensations like touch and warming. For people with allodynia, a condition where minor sensations can cause severe pain, targeting DORs with medication can reduce pain.

<http://www.drugabuse.gov/news-events/news-releases/2014/03/targeting-delta-opioid-receptor-may-reduce-pain-without-causing-addiction>

**April 3, 2014** - *Medication can help prevent relapse in cocaine-dependent males.* NIDA released the results of a new study showing that the medication baclofen can help prevent relapse in cocaine-dependent males. Drug cues, even subliminal ones, can trigger people with drug addiction to seek and participate in drug use. The drug baclofen, which is commonly used to prevent spasms in patients with spinal cord injuries and neurological disorders, interferes with the brain's early response to these subliminal drug cues and can stunt the internal processing of drug-related cues that can lead to relapse.

<http://www.drugabuse.gov/news-events/news-releases/2014/04/medication-can-help-prevent-relapse-in-cocaine-dependent-males>

**April 4, 2014** - *Web-based intervention strengthens drug abuse treatment.* A new study showed that incorporating the web-based Therapeutic Education System (TES) intervention in the treatment of drug abuse can not only help people stop using drugs, but can also keep them in treatment longer. TES is a web-based version of the Community Reinforcement Approach plus Contingency Management, a packaged approach with demonstrated efficacy. NIDA funded this study.

<http://www.drugabuse.gov/news-events/news-releases/2014/04/web-based-intervention-strengthens-drug-abuse-treatment>

### **Interview Highlights: January 2014 - March 2014**

*Associated Press* - Dr. Nora Volkow was interviewed about heroin.

*Bloomberg* – Dr. Ivan Montoya was interviewed about vaccines.

*Boston Globe* – Dr. Susan Weiss was interviewed about marijuana; Dr. Wilson Compton was interviewed about prescription drug abuse.

*Financial Times* – Dr. Volkow was interviewed about heroin.

*Men's Journal* - Dr. Wilson Compton was interviewed about addiction.

*National Geographic* – Dr. Volkow was interviewed about heroin.

*NPR* – Dr. Marilyn Huestis was interviewed about drug testing.

*NPR Diane Rehm Show* – Dr. Compton was interviewed about heroin.

*Shape Magazine* – Dr. Joe Frascella was interviewed about compulsive overeating.

*The Los Angeles Times* - Dr. Compton was interviewed about heroin.

*The New York Times* – Dr. Huestis was interviewed about drugged driving. Dr. Volkow was interviewed about medical marijuana.

*The Palm Beach Post* – Dr. Steve Gust was interviewed about marijuana.

*Time Magazine* – Dr. Nora Volkow was interviewed three times: about K2/Spice, opioids and heroin.

*US News & World Report* - Drs. Volkow and Compton were interviewed about heroin.

*Washington Post* - Dr. Volkow was interviewed about heroin.

*Washington Times* - Dr. Compton was interviewed about heroin.

*NPR's The Diane Rehm Show* - Dr. Volkow was interviewed about marijuana.

## MEETINGS/CONFERENCES

NIDA staff delivered two sessions at the **2014 Community Anti-Drug Coalitions of America (CADCA) National Forum** at National Harbor, MD, February 3-6, 2014. Ruben Baler, Ph.D. (NIDA) presented “Where do Addictions Come from?” and Jacqueline Lloyd, Ph.D., (NIDA) chaired a session on “Cultural and Contextual Adaptation of Evidence-Based Prevention Interventions for Real World Community and Practice Settings.” The sessions highlighted the ongoing research being conducted by Dr. Jeanne Poduska (American Institutes for Research, Baltimore, MD) on the Good Behavior Game, which is an evidence-based classroom behavior management strategy. Dr. Volkow delivered a plenary address, and Drs. Wilson Compton and Jack Stein participated in a Power Session titled “Science Update from NIDA: Spotlight on Marijuana-Related Research.”

On March 13, 2014, NIDA participated in the 15<sup>th</sup> annual **Brain Awareness Week** activities at the National Museum of Health and Medicine. NIDA staff members Drs. Cathrine Sasek, Roger Sorensen, Rik Kline and Erica Boone led the “**Brain Derby**,” an interactive fast-moving game designed to teach children about drugs of abuse and neuroscience, with children from area schools as part of the week-long festivities. NIDA’s game was enthusiastically received and the children not only learned new things, but they also had a great time.

On April 24, 2014 NIDA again participated in **Take Your Child to Work Day** by having numerous activities both in the Neuroscience Center and on the main NIH campus. Activities included: **Brains Up Close, Animal Brain Matching, Looking through the Microscope, Hands on Science, Brain Science Coloring Contest, Sharpen Your Brain, Dr. Sciencehead** and **Brain Derby**. In addition, this year NIMH partnered with NIDA to include an activity, **Put on Your Thinking Cap** and Archie Fobbs from the National Museum of Health and Medicine gave an interactive presentation titled **Your Brain – How It Works And What Happens When It’s Injured**. A very enthusiastic group of children was able to rotate through the stations and learn about the brain as well as how drugs can impact the brain and body. NIDA and NIMH staff who developed and led the activities included Drs. Cathrine Sasek, Mary Kautz, Sheri Grabus, Dave Thomas, as well as Stephanie Older, Quandra Scudder, Hirsch Davis, Rachel Wolf and Phyllis Quartey-Ampofo.

On April 25-27, 2014, NIDA participated in the 3rd annual **USA Science & Engineering Festival** at the Washington DC Convention Center. The festival, which was designed to re-invigorate the interest of our Nation’s youth in science, presented the most exciting, educational and entertaining science available. NIDA staff, led by Dr. Cathrine Sasek, conducted the **Brain Derby** (see above) and other activities to educate youth about what makes the human brain different from the brains of other species, as well as what areas of the brain are involved in and impacted by drugs of abuse.

On February 10-11, 2014, NIDA’s Office of Diversity and Health Disparities (ODHD) hosted a two-day **Special Populations Research Development Seminar Series Workshop** at NIDA Headquarters in Rockville, Maryland. Chaired by Flair Lindsey, Program Analyst, this workshop convened 18 new early stage substance abuse investigators and NIDA-supported faculty mentors in an intensive grants development workshop setting. During the workshop, new investigators learned of NIDA’s research and funding priorities and the NIH grants submission and review process, met with NIDA program staff and NIDA funded researchers and received feedback on research proposals.

NIDA's Office of Diversity and Health Disparities (ODHD) convened the **NIDA ODHD Translational Research Speaker Series: Promoting Diversity and Moving Toward Health Equity** at NIDA Headquarters in Rockville, Maryland, on Tuesday, March 11, 2014. Featured speaker Dennis M. Donovan, Ph.D., Director Alcohol and Drug Abuse Institute & Professor, Psychiatry and Behavioral Sciences, University of Washington School of Medicine, presented "A Community-Based Participatory Research (CBPR) Perspective on Moving Evidence-Based Drug Treatment Research into Clinical Practice." His presentation provided an overview of issues involved with moving Evidenced Based Practices into community based settings, with an example and issues drawn from the Clinical Trials Network and from work with Native American communities. This was the 5<sup>th</sup> seminar of the ongoing series, which is coordinated by Flair Lindsey, Program Analyst, ODHD.

NIDA's Office of Diversity and Health Disparities (ODHD) convened a two-day **NIDA Diversity Supplements Workshop** on Thursday and Friday, April 10-11, 2014 at NIDA Headquarters in Rockville, Maryland. The workshop brought together 26 current NIDA and selected NIAAA-supported diversity supplement recipients at the pre-doctoral, postdoctoral, and early career investigator levels, and presented them information and guidance on NIDA research priorities and research funding opportunities to help them transition to independent research careers. Participants met with NIDA and NIAAA program staff and senior officials, and with NIDA-funded investigators, some of whom were former recipients of NIDA diversity supplement funding support. In addition, participants presented posters of research they currently are engaged in through their respective diversity supplements. Pamela Goodlow, Public Health Analyst, ODHD, hosted and coordinated the two-day workshop. Dr. Albert Avila, Acting Director, ODHD, presented "Health Disparities Research at NIDA and the NIH" and "Research Training Opportunities Available through NIDA/NIH."

From November 2013 to March 2014, the IRP Office of Education and Career Development, together with the NIH Office of Intramural Training and Education, have offered the following workshops or seminars: Improving Spoken English; Giving an Effective Scientific Talk; Preparing for the MCAT and GRE; Scientists Teaching Science (9-week course); Workplace Dynamics (Conflict and Feedback, Team Skills, Diversity); How to Succeed in Graduate School; Introduction to Grant Writing; EndNote and Reference Manager Training; Approaches to Mentoring (3-week seminar); FARE Abstract Workshop; Writing Courses (Basic Science Writing and Publishing a Scientific Paper); Creating and Presenting an Award-Winning Poster; Industry Job Search; and Skill Blitz sessions on Networking, Career Satisfaction and Success, and Interviewing.

The **NIDA National Drug Abuse Treatment Clinical Trials Network (CTN) Steering Committee Meetings** were held March 11-13, 2014 in Gaithersburg, Maryland. During the meeting, the CTN Minority Interest Group provided a workshop titled "Funding Opportunities for Advancing Substance Abuse Treatment for Racial/Ethnic Minorities," and the CTN Design and Analysis Workgroup's workshop was titled "Alternative & Innovative Clinical Trial Designs." During the main Steering Committee Meeting, attendees were provided an update on the activities of the Committees (Executive, Research Development, Research Utilization and Publications), and two symposia — "SBIRT for Substance Use Disorder," and "Transforming the Clinical Trials Enterprise to Meet the Needs of Health Care Reform." The following meetings convened:

Special Interest Groups

- Adolescent
- Pharmacotherapy
- Registry
- SBIRT

## Workshops & Forums

- Design & Analysis Workshop
- International Forum
- Minority Special Interest Group

## Caucuses and Committees

- CTP and PI Caucuses
- Executive Committee
- Node Coordinator Workgroup
- Research Utilization Committee
- Research Development Committee
- Steering Committee

## Study Team Meetings

- CTN 0049, Project HOPE
- CTN 0053, ACCENT
- CTN 0054, ADAPT
- CTN 0056-Ot, Testing and Linkage to HIV Care in China
- CTN 0057-Ot, SBIRT-PC

### **NIDA's Blending Initiative-Supported Sessions**

A Regional Conference was held March 20-21, 2014 in Towson, Maryland by the Mid- Atlantic and Delaware Valley CTN Nodes and the Central East Region ATTC with support from the Blending Initiative. The title of the conference was "Preparing for Change: Emerging Models for Integrated Health Care Delivery."

The Society for Adolescent Health and Medicine (SAHM) Annual Meeting was held March 23-26, 2014 in Austin, Texas. The Blending Initiative sponsored a session titled "Screening and Brief Intervention of Adolescent Substance Use in Primary Care."

The American College of Physicians (ACP) Annual Internal Medicine Conference was held April 10-12, 2014 in Orlando, Florida. The Blending Initiative sponsored a session titled "Motivational Interviewing: Skills to Engage Patients and Initiate the Discussion of Substance Abuse in Internal Medicine."

The Annual Medical-Scientific Conference of the American Society for Addiction Medicine (ASAM) was held April 10-13, 2014 in Orlando, Florida. The Blending Initiative provided support for a session titled "Prescription Stimulant Use and Misuse Among Youth: Review and Practice Implications."

Operation Unite's National Rx Drug Abuse Summit was held April 22-24, 2014 in Atlanta, Georgia. The Blending Initiative provided support for a symposium titled "What's Next for Treatment?"

The Society for the Teachers of Family Medicine (STFM) held its Annual Spring Conference May 3-5, 2014 in San Antonio, Texas. The Blending Initiative sponsored a day-long workshop titled "Empowering Family Medicine Residencies to Address Prescription Opioid Abuse With Office-Based Buprenorphine Treatment."

Dr. Jack Stein, Director, OSPC, participated in a Healthy People 2020 Progress Review Webinar entitled “Substance Use and Mental Disorders: Early Detection, Prevention and Treatment” in Washington, DC on February 26, 2014.

Dr. Jack Stein presented “Prescription Drug Abuse: It’s Not What the Doctor Ordered” at the Tri-County Oral Facial Surgeons Study Group in State College, PA on March 19, 2014.

Dr. Ruben Baler, OSPC, participated in the Mentor Foundation’s “Shattering the Myths: An Interactive Youth Drug Abuse Prevention Rally” at the Sweden House, Washington D.C. on January 30, 2014.

Dr. Baler participated in a Q&A and panel discussion on the science of addiction at a National Drug Facts Week at the 4H Country Club in Chevy Chase, MD on January 30, 2014.

Dr. Ruben Baler lectured on the “Neuroscience of Addiction and Resilience, at the Drug Awareness freshman course in the Scholl of Public Health, Georgetown University, Mt Vernon Campus, Washington D.C. on February 2, 2014.

Dr. Ruben Baler presented “The Science of Addiction: Building Resilience from the Brain Up” at CADCA’s 24<sup>th</sup> National Leadership Forum. Gaylord Hotel, Washington D.C. on February 6, 2014.

Dr. Albert Avila, Acting Director, Office of Diversity and Health Disparities (ODHD), presented at the National Drug Abuse Treatment Clinical Trials Network meeting on “Funding Opportunities for Advancing Substance Abuse Treatment for Racial/Ethnic Minorities” on March 11, 2014 in Gaithersburg, Maryland. This workshop aimed to raise interest and opportunities in the clinical field for individuals who are interested in applying for independent funding support.

Dr. Susan Volman, DBNBR, served as the NIDA representative for the development of and proposal evaluation for the interagency FOA reissue “Collaborative Research in Computational Neuroscience (CRCNS) Innovative Approaches to Science and Engineering Research on Brain Function” Through the CRCNS program, the National Science Foundation (NSF), the National Institutes of Health (NIH), the German Federal Ministry of Education and Research, the French National Research Agency, and the United States-Israel Binational Science Foundation support collaborative activities to advance the understanding of nervous system structure and function, mechanisms underlying nervous system disorders, and computational strategies used by the nervous system.

Dr. Minda Lynch, DBNBR, served on a panel in the Pathways to Careers in Science workshop at The University of Texas Health Science Center at San Antonio in March, 2014. This early career development session preceded UT San Antonio’s Behavior Biology and Chemistry Meeting with a theme in 2014 of “Translational Research in Addiction”.

Dr. Yu (Woody) Lin, DCNBR, was invited by the American Academy of Pain Medicine to organize, moderate and present at a workshop session entitled “NIH Pain Research: Optimizing Funding through Grant Writing”. The conference was held at the society’s 31<sup>th</sup> annual conference on March 7-9, 2014 in Phoenix, AZ.

Dr. Samia Noursi, DCNBR and Deputy Coordinator, Women and Sex/Gender Differences Research Program was invited by SAMHSA to join the new strategy development initiative, General Adult Trauma Screening and Brief Intervention in Primary Care and Public Health Settings” (GATSBI). The goal of GATSBI is to build a framework for developing a model for screening and brief intervention

for trauma in primary care and other health/public health settings. Led by SAMHSA, the effort includes researchers, practitioners, people with lived experience of trauma and federal policymakers. Kick off meeting was held on March 10-11, 2014 at SAMHSA's headquarters, Gaithersburg, MD.

Dr. Samia Noursi was invited to speak at the SAMHSA Advisory Committee for Women's Services on April 2, 2014.

At the February 12, 2014 meeting of NIH's Office of Research on Women's Health (ORWH) Coordinating Committee for Research on Women's Health (CCRWH), Dr. Cora Lee Wetherington, DCNBR and Women and Sex/Gender Differences Research Program Coordinator, gave a talk on NIDA's 2011-2012 Biennial Report to Congress. Dr. Wetherington is NIDA's representative to the CCRWH. NIDA's report was part of ORWH's mandated biennial report to Congress.

Dr. Cora Lee Wetherington was a poster judge for the Women's Health 22nd Annual Congress in Washington, DC, April 4-6, 2014.

Dr. Cora Lee Wetherington represented NIDA at the 2014 Annual Meeting of the Organization for the Study of Sex Differences, April 24-26, 2014, Minneapolis, MN.

Dr. Cora Lee Wetherington represented NIDA on April 1, 2014, at FDA's, public hearing on the *Food and Drug Administration Safety and Innovation Act (FDASIA) Section 907* which directed FDA to report on the extent to which subgroups participate in FDA clinical trials that support applications for new drugs, biologics, and devices, and specifically, whether reports of subgroup safety and effectiveness are reported to FDA in a manner consistent with FDA requirements and guidance, and whether and how safety and effectiveness data by subgroup is eventually made public. The hearing was based upon FDA's August 13, 2013 report, Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products.

On February 10-12, 2014, Dr. Cheryl Anne Boyce, DCNBR, served as a science, technology, engineering and mathematics (STEM) assessor for the new track of the Presidential Management Fellow (PMF) program interview session.

Dr. Cheryl Anne Boyce participated in the MacArthur Foundation invited meeting on Evidence Based Practices (EBPs) in Communities of Color convened on February 26, 2014 in Chicago, IL.

Dr. Cheryl Anne Boyce presented a talk entitled "Presentations from Invited Federal Agencies: Collection of Behavioral and Health Outcome Data" at the National Children's Study Federal Consortium meeting on March 10, 2014 at the Natcher Conference Center, NIH Main Campus, Bethesda, MD.

Dr. Cheryl Anne Boyce attended the 2014 Society for Research on Adolescence (SRA) Biennial Meeting in Austin, TX on March 20-21, 2014. During the SRA Young Scholars Program Preconference meeting, she presented a research grant skills workshop and Dr. Kathy Etz (DESPR) joined the discussion panel. She also presented at an invited roundtable session for the Emerging Scholars on "Early Career Grant Writing" and moderated the panel of NIDA staff including Dr. Aria Crump (DESPR), Dr. Kathy Etz (DEPSR) and Tisha Wiley (DESPR) at the session.

Dr. Cheryl Anne Boyce attended the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD) on April 1-2, 2014.

Dr. Cheryl Anne Boyce chaired the discussion hour session entitled “Research and Policy in Action with SRCD Policy Fellows: Perspectives of Alumni” at the SRCD 2014 Special Topic Meeting: Strengthening Connections among Child and Family Research, Policy and Practice, on April 4, 2014, Alexandria, VA with participants Drs. Tisha Wiley, DESPR, LeShawndra Price, NIMH, Valerie Maholmes, NICHD, and Dara Blachman-Demner, Department of Justice.

Dr. Karen Sirocco, DCNBR, participated in the Pediatric HIV/AIDS Cohort Study (PHACS) 2014 Spring Leadership Retreat held on March 20-21, 2014 at the Bolger Conference Center in Bethesda, MD.

Dr. Redonna K. Chandler, Acting Director, DESPR presented a plenary entitled, Understanding Addiction as a Brain Disease: Judicial Interventions to Shape Behavior at the Vanderbilt Colloquium on Law, Neuroscience, and Criminal Justice Meeting, Nashville, TN, February 6-7, 2014.

Dr. Redonna K. Chandler chaired a panel entitled, Seek, Test, Treat, and Retain: Addressing HIV in the Criminal Justice System at the 7<sup>th</sup> Academic & Health Policy Conference on Correctional Health, Houston, TX, March 20-21, 2014.

Dr. Redonna K. Chandler chaired a panel entitled, Improving Implementation of Best Practices in Correctional Settings: An Overview of Conceptualization, Design, and Measurement at the 7<sup>th</sup> Academic & Health Policy Conference on Correctional Health, Houston, TX, March 20-21, 2014.

Dr. Redonna K. Chandler chaired a panel entitled, Opioid treatment and CJS Settings: Jail-Based and CJ-DATS Intervention at the 7<sup>th</sup> Academic & Health Policy Conference on Correctional Health, Houston, TX, March 20-21, 2014.

Dr. Redonna K. Chandler presented a plenary entitled, Prevention and Treatment of HIV/AIDS among Drug Using Populations: Research Priorities at NIDA at the 4<sup>th</sup> International HIV Treatment as Prevention Workshop, Vancouver, British Columbia, April 1-4, 2014.

Dr. Redonna K. Chandler presented on, The Harmonization of HIV Research Protocols: the NIDA Experience, at the 4<sup>th</sup> International HIV Treatment as Prevention Workshop, Vancouver, British Columbia, April 1-4, 2014.

On February 3, 2014, Dr. Harold Perl, DESPR, Prevention Research Branch organized and chaired a session titled, “Prevention in the Era of Health Care Reform,” at CADCA's 24th National Leadership Forum, in National Harbor, MD.

On February 5, 2014, Dr. Marsha Lopez, DESPR, Epidemiology Research Branch presented an update on NIDA’s Marijuana Policy Research portfolio to the Second Joint Meeting of NIAAA, NIDA and NCI Councils in Bethesda, MD.



On February 10-11, 2014, Drs. Dionne Jones, DESPR, Services Research Branch and Sarah Duffy, participated in the NIDA Research Development Seminar series sponsored by the Office of Diversity and Health Disparities, in Bethesda, MD.

On January 23, 2014, Dr. Jacqueline Lloyd, DESPR, Prevention Research Branch presented on a panel titled “Future Directions and Funding Priorities for HIV and Technology-Based Research” at the UCLA Center for HIV Identification, Prevention and Treatment Services (CHIPTS) Conference “Innovative Use of Technology for HIV Prevention and Care: Evidence, Challenges, and the Way Forward”, held in Los Angeles, California.

On January 16, 2014, Dr. Jacqueline Lloyd served on a NIH panel and presented at a workshop titled “Research Opportunities at NIH” during the Society for Social Work Research Annual Conference in San Antonio, Texas.

On January 23, 2014, Dr. Eve Reider, DESPR, Prevention Research Branch gave an invited opening presentation on “Strategic Frameworks for Behavioral Health Research” at a Marine Corps Behavioral Health Branch Research Summit at Marine Corps Base, Quantico, VA.

Dr. Eve Reider is a member of the Institute of Medicine-National Research Council Forum on Promoting Children’s Cognitive, Affective, and Behavioral Health. The first meeting took place January 13, 2014, at the National Academy of Science Building, Washington, D.C.

On February 6, 2014 and April 3, 2014, Dr. Eve Reider participated in the development of the second Joint Defense Health Program, VA, DOE, and NIH Psychological Health and Traumatic Brain Injury Portfolio Review and Analysis that was held at Fort Detrick, MD. Dr. Reider presented on an integrated approach for strategic research planning for substance abuse that was organized on a research continuum framework (basic science, epidemiology, etiology, prevention, treatment, and services) across the DoD, VA, NIDA, and NIAAA.

On February 5, 2014, Dr. Augusto Diana, DESPR, Prevention Research Branch organized and chaired a session titled, “Preliminary Outcomes from the SPF SIG Cross-site Evaluation, Cohorts I and II,” at CADCA's 24th National Leadership Forum, held at National Harbor, MD.

On February 11, 2014, Dr. Augusto Diana moderated a panel at the meeting, The House That Evidence-Based Practice Built: Moving from Program Development to Real World Outcomes in Washington, DC. The meeting featured representatives of model programs, federal agencies, private foundations, and others in an effort to maximize opportunities to disseminate effective prevention programs.

On February 14, 2014, Dr. Augusto Diana represented NIDA at a Briefing to the Congressional Addiction, Treatment and Recovery Caucus and the Congressional Caucus on Prescription Drug Abuse, featuring talks about Prevention Programs for Addiction and Substance Abuse. The briefing was held at the Rayburn House Office Building in Washington, DC and was attended by community coalition representatives presenting to members of Congress about the effectiveness of their community prevention efforts.

Dr. Jag Khalsa, DPMCD, was invited by the University of Massachusetts Dartmouth Chancellor to give a talk to the junior and senior faculty and graduate students on the Role of Biotechnology

(nanotechnology) in Drug Addiction and Co-occurring Infections, ongoing research at NIDA, and funding opportunities available at NIDA/NIH, March 5-6, 2014.

Drs. Jag Khalsa and Jeffrey Samet chaired a symposium at the ASAM Annual Conference in Orlando FL in April 2014 on Neuropsychiatric Consequences of Viral Hepatitis C Infection in Drug Abusers.

Dr. Jag Khalsa participated in another ISAM/ASAM collaborated symposium on Treatment of Dual Infections in Drug Abusers in domestic and international settings.

Drs. Ivan Montoya, DPMCD, and Gavin Bart co-chaired a symposium on Biologics to Treat Drug Addictions at the ASAM Annual Conference.

Dr. Amy Newman, IRP, chaired and presented in a session entitled “Traversing the Translation of Target-based Hypotheses in Psychostimulant Addiction” at the Winter Conference on Brain Research (WCBR) in Steamboat Springs, CO in January 2014. Dr. Newman was also elected to the WCBR Board of Directors at the January meeting.

Dr. Amy Newman presented the keynote lecture at the University of Michigan Pharmacological Sciences Training Program Annual Symposium in Ann Arbor, MI in March 2014.

Drs. Oluyomi Okunola-Bakare, Thomas Keck, Comfort Boateng, and Vivek Kumar, IRP, all won travel awards to present at the 2014 Behavior, Biology and Chemistry: Translational Research in Addiction meeting in San Antonio, in March. Dr. Keck won the best presentation award at this meeting.

Dr. Bruce Hope, IRP, was invited to speak at The University of Texas at Austin Waggoner Center for Alcohol and Addiction Research in Austin, TX on February 24, 2014.

Dr. Stephen Heishman, Director, Office of Education and Career Development, IRP, participated in an early career panel discussion at the annual meeting of the Society for Research on Nicotine and Tobacco (SRNT) in Seattle in February 2014. He was also invited to be the advisory co-chair of the Trainee Network of SRNT.

Dr. Yavin Shaham gave invited lectures at the University of Arizona and Marquette University.

Dr. Michael Baumann, IRP, was invited to give lectures for the NIDA/IRP-Johns Hopkins University Substance Abuse and Co-Morbidities Course and for the NIDA/IRP Fellows Research Lunch.

On February 25, 2014, Dr. Baumann gave a presentation entitled, “Pharmacology of cathinone analogs that are structurally-related to MDMA (Ecstasy)”, for the Neurosciences Seminar Series at Harvard University, McLean Hospital, in Belmont MA.

Dr. Kenner Rice, IRP, was the invited special plenary lecturer at the Brain, Behavior, and Chemistry Translational Research in Addiction Conference, San Antonio, TX, March 2014.

Dr. Jean Lud Cadet, IRP, presented a talk entitled “Epigenetics and transcriptional bases of methamphetamine addiction” at Howard University on March 19, 2014.

Dr. Jean Lud Cadet, the Diversity and Outreach Committee, and SDFDR Fellows attended the Baltimore City Science Fair on March 22 and 23, 2014. Five awards from NIDA IRP were presented to students based on scientific merit.

Dr. Marilyn Huestis, IRP, and other NIDA representatives presented current CDM research efforts in the area of drugged driving to the National Transportation Safety Board on February 12, 2014. The NTSB has made drugged driving one of their strategic issues for the coming years.

Dr. Jonathan Katz, IRP, presented an invited lecture within a plenary symposium entitled: “Non-classical pharmacology of the dopamine transporter and addiction” at the Sixth Annual Behavior, Biology and Chemistry: Translation Research in Addiction Conference, March 15-16, 2014.

Dr. Amina Woods, IRP, chaired a symposium on “Therapeutic Aspects of Molecular and Cellular Neuroscience” at the 2nd International Conference on Neurology and Therapeutics in Chicago, June 17-19, 2013.

Dr. Amina Woods gave a lecture on “How MS Analysis in General and Innovative Imaging MS Sheds Light on What’s Happening in Traumatic Brain Injury,” Johns Hopkins School of Medicine, Pharmacology and Molecular Sciences seminar.

Dr. Amina Woods presented a seminar entitled “Rules of engagement: Intracellular domains as determinants of receptor heteromers” at George Mason University in Virginia.

Dr. Geoffrey Schoenbaum, IRP, gave invited lectures at the University of Michigan, and Caltech.

Dr. Elliott Stein, IRP, spoke at the California Institute of Technology, Pasadena, CA on “Imaging, genetics, and nicotine addiction” in March 2014.

## **PLANNED MEETINGS**

*\* (Pending approval)*

### **College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting - San Juan, Puerto Rico, on June 14–19, 2014. \***

The National Institute on Drug Abuse (NIDA) will sponsor a Grant-Writing and Career Development Workshop at the CPDD Annual Scientific Meeting. The Grant/Career Workshop provides new or junior investigators with information and skills to advance their research careers, with a heavy emphasis on NIDA funding opportunities, grantsmanship, and the grant application process. In addition, NIDA's Blending Initiative will provide support for a session titled "Addiction Treatment Research vs Usual Care: What are the Foreseeable Risks?"

### **2014 American Psychiatric Association Annual (APA) Meeting – New York, NY, May 3-7, 2014. \***

NIDA will hold a track of sessions at the APA Annual Meeting. Dr. Nora Volkow is scheduled to deliver the Frontiers of Science Lecture, and hold an interactive session with residents. NIDA staff will chair sessions on a variety of substance abuse related topics including: Cannabis Use and Youth: Risk Assessment and Implications for Clinical Practice, The Role of Substance Use in Violence Against Self and Others, Persistence and Desistance of Comorbid Drug Abuse and Psychiatric Disorders in Adolescence, Biological Approaches To Treat Substance Use Disorders, and Diagnostic and Assessment Considerations for the Treatment of Comorbid Opioid Addiction and Chronic Pain.

### **2014 American Psychological Association (APA) Annual Meeting – Washington, DC, August 7-10, 2014. \***

NIDA will co-host the NIDA/NIAAA /APA (Divisions 28&50) Early Career Investigator Poster Session.

## **STAFF HIGHLIGHTS**

### **Staff Honors and Awards**

**Dr. Elizabeth Robertson**, DESPR, has been selected to receive the Society for Prevention Research's (SPR) *2014 Presidential Award* for her outstanding contributions to advancing the field of prevention science. The SPR *Presidential Award* is given to an individual or a team of individuals who have made a major specific contribution to prevention science research. This award is a "lifetime achievement" award for a significant body of research or theory in any area related to prevention that has had a major impact on the field. Dr. Robertson will be presented this award at the Annual Awards Presentation on Thursday, May 29, 2014 at the 22<sup>nd</sup> Annual Meeting of the Society for Prevention Research.

**Dr. Guillermo Esber**, IRP, was awarded a K99 grant.

**Dr. Marilyn Huestis**, CDM Chief, IRP, was selected for the new National Commission on Forensic Science that will set the standards for all forensic sciences in the United States.

**Dr. Jag Khalsa**, DPMCDA, received the *Lifetime Contributions Award* from the Society on NeuroImmune Pharmacology, March 26-29, 2014.

**Dr. Belinda Sims**, DESPR, Prevention Research Branch, received a Meritorious Research Service Commendation for 2013 from the American Psychological Association Board of Scientific Affairs. The commendation recognizes individuals who have made outstanding contributions to psychological science through their service as employees of the federal government or other organizations. Dr. Sims was recognized for her outstanding contributions to psychological science through her service as a research and health science administrator NIDA.

**Dr. Dong Wang**, IRP, received a travel award for a Janelia Farm Conference on Genetic Manipulation of Neuronal Activity III held May 18-21, 2014.

**Dr. Roy Wise**, IRP, joined the Program Committee of the Society for Neuroscience.

**Dr. Ariane Wohlfarth**, Visiting Fellow, IRP, was awarded the 2014 Excellence in Scientific Research NIDA Fellow Award by the NIA and NIDA Women Scientists Advisor Committee..

### **Staff Changes**

#### **New Employees**

**Gloria Dabbondanza** joined the Administrative Management Branch (AMB) on February 10, 2014 as a Program Analyst. She will be the new NIDA HR liaison and will also be responsible for workforce development programs and activities. Prior to joining the NIDA team, Gloria was a Paralegal Specialist for the Civil Rights Division of the Department of Justice, and then moved to the National Heart, Lung, and Blood Institute as a Management Analyst in 2007. She has experience in policy development, budget management, human resource liaison, program evaluation, data management and reporting, editing, and event planning.

**Stacey Gills** joined NIDA on March 13, 2014 as the Chief of OM's Administrative Management Branch (AMB). Stacey comes to us from the NBS group in the NIH OD where she has been a Change Management Specialist facilitating business system operations and rollouts. Stacey previously served as a Lead Administrative Officer at NCI and a Program Analyst at NIAID, and is experienced at advising senior management on operations, policy, change, and productivity. She holds a degree in Sociology from Towson State University and has received numerous awards recognizing her performance and leadership.

**Debasis Goswami** joined NIDA on February 24, 2014, as IRMB's Applications Manager within the Office of Management. Debasis comes to us with 20+ years of extensive experience with Program and Project Management handling multiple IT initiatives varying in size and scope spanning geographical boundaries across the world. He has strong hands-on experience in a diverse set of technologies along with a strong sense of focus around Customer Relationship Management. A recent NIH Director's Award recipient, Mr. Goswami comes to NIDA from NIDDK where he supported many different stakeholder communities including Scientific and Grants Management Divisions since 2009. In addition to supporting Administrative Systems at NIDDK, Mr. Goswami also has a strong understanding of and experience in the Pharmaceutical industry focusing on drug development and Clinical Trials of all stages, Regulations, and Data Management. At NIDA, Debasis will play an essential role in managing the Operations & Maintenance and New Project Development activities within our Application Management team supporting NEPS, CMIS, DISCS, CAS, and SharePoint Applications.

**Dr. Hiromi Ono** joined OEA as a Scientific Review Officer in February 2014. Hiromi received bachelor's degrees in mathematics and sociology from Reed College and master's and doctoral degrees in demographics and sociology from UCLA and UC Berkeley. She was a postdoctoral fellow at the School of Public Affairs, UCLA, an assistant research professor at the University of Michigan, and a tenured associate professor of sociology at Washington State University and her 35 publications address family demography, methodology and related policy issues. Hiromi joined the government as a program officer for the Postsecondary Education and the Improving Education Systems programs at the Institute for Education Sciences, US Department of Education.

**Christina Page** joined OEA as an Extramural Support Assistant in February 2014. Christina transferred from the Department of Army where she worked as a Patient Representative for Moncrief Army Community Hospital, one of the largest basic trainee locations in the nation. She received her undergraduate degree in Business Administration from Frostburg State University. Christina had previously worked for NINDS as a human resource intern in the Presidential Management Fellows Program and brings experience in employee relations in the public sector with the DHHS and Department of Army as well as private sector experience as a Managed Care Specialist representing Cape Fear Valley Health System in North Carolina.

**Dr. Jagadeesh Rao** joined NIDA in January 2014 as a Scientific Review Officer. Jagadeesh received bachelor's and master's degrees in biochemistry and a doctoral degree in neurochemistry from the University of Mysore and NIMHANS, India. After a postdoctoral fellow position at the University of Illinois, Jagadeesh was a scientist with Johnson and Johnson in Pennsylvania. He joined NIH's National Institute of Aging as a Research Fellow and was promoted to Staff Scientist. Jagadeesh's 68 publications address neuroinflammation, imaging, neurotransmitter transporters, transduction, behavior and pharmacology, with attention to synaptic plasticity, HIV, and signal transduction related to chronic neurological diseases.

**Christine Salaita**, MS, RDN, joined NIDA's OEA as a Program Analyst in April 2014. She will assume primary responsibility for NIDA's National Advisory Council activities. Christine came to NIDA from NIDDK, where she was a Program Analyst in the Division of Extramural Activities for 3 ½ years and was responsible for Council activities, end-of-year reporting and helped ensure timely processing and publication of FOAs. Prior to that, Christine completed a 2-year competitive NIH Management Intern program with rotations through multiple Institutes and with the State Department in the Office of the Global AIDS Coordinator, focused on the administrative management of international and global health initiatives. Her first position at NIH was as a Clinical Research Dietitian in the Department of Nutrition at the Clinical Center where she provided medical nutrition therapy and counseling to patients with immunodeficiency including HIV/AIDS, diabetes, renal disease and transplantation, obesity and sickle cell disease, precepted dietetic interns, co-authored research publications, and presented to outside organizations.

### **New Appointments/Transfers**

**Dr. Albert Avila** has been selected for the position of Director of NIDA's Office of Diversity and Health Disparities (ODHD). Dr. Avila received his Ph.D. from Georgetown University and completed his postdoctoral training at the National Institute of Dental and Craniofacial Research (NIDCR). At NIDCR, he became the Intramural Training Director and then a Program Officer (PO) directing extramural research training and career development. Dr. Avila came to NIDA's DCNBR where, as a PO, he directed a grant research portfolio in neuroimmunology, psychopharmacology, and HIV as they relate to drug abuse, and fostered a robust research training and career development portfolio for early career investigators. Since June 2013, he has been serving as Acting Director, ODHD. Dr. Avila brings with him an extensive background in research training, career development, and health disparity issues, along with passion and enthusiasm for drug and addiction research. Please join me in welcoming Dr. Avila to his new role at NIDA where he will use his outstanding creativity and leadership to increase our ability to recruit and retain the best scientists at the NIH.

**Nathaniel Fredericks** has been selected for the position of Chief, Management Analysis Branch (MAB) in the NIDA Office of Management. Since joining NIDA in February of 2013, Nathaniel has played a key role in transitioning the Conference Approval function to MAB. He has also guided NIDA's Risk Management program and served as the administrator for the NIDA IT Change Review Board. Nathaniel holds Bachelor's and Master's degrees in accounting from Saint Louis University, and has had a diverse career ranging from positions as the finance director for political campaigns, corporate tax consulting, an internal auditor for St. Louis County Government, and the audit remediation lead for the Division of Payment Management in the Program Support Center of HHS.

**Dr. Cheryl Anne Boyce**, DCNBR, will serve as the representative for NIDA as an official member of the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD). **Dr. Karen Sirocco**, DCNBR, will serve as the alternate representative.

**Dr. Mary Kautz**, DCNBR, has been appointed as the NIDA Coordinator for the NIH-FDA Tobacco Regulatory Science Program (TRSP). In this role, she serves as a Liaison between NIDA and NIH TRSP-OD staff to administer grant awards that have been funded by the Food and Drug Administration (FDA) Center for Tobacco Products (CTP) to inform the development and evaluation of regulations on tobacco product manufacturing, distribution, and marketing.

## **Departures**

**Dr. Eliane Lazar-Wesley**, OEA, moved to the Scientific Review Branch at NIDCD in April 2014. For 11 years Eliane effectively managed many types of reviews as an SRO at NIDA, notably serving as the SRO for NIDA-K, the Training and Career Development Review Committee, and for the Centers reviews.

**Cikena Reid**, Program Analyst, OEA, moved to the White House Liaison Office at the USDA in March 2014. For the past 5 years, Cikena's primary responsibility was managing the activities of NIDA's National Advisory Council. Notably, she was responsible for introducing the Electronic Council Book into Council operations.

**Dr. Mihaela Iordanova**, IRP, accepted a Tier II Chair position at Concordia University in Montreal.

**Dr. Jim Bjork**, DCNBR, has accepted a position as Associate Professor in the Department of Psychiatry of the Virginia Commonwealth University Medical School in Richmond, Virginia, effective July 2014. Jim will also have a part-time appointment at the McGuire VA Hospital in Richmond. In his new position, Jim will continue his neuroimaging research on the functional mechanisms of altered motivation, impulse-control, and decision-making in addiction- both in community and campus populations, as well as in veterans with and without traumatic brain injury. Jim joined NIDA in 2007, after several years conducting neuroimaging research on alcoholic inpatients and their adolescent children at the NIH Clinical Center, as a postdoctoral fellow in the NIAAA Laboratory of Clinical and Translational Studies. Jim intends to continue to be of service to his NIDA colleagues until his July departure, as well as in the future, in the capacity of an extramural researcher.

## **Retirements**

**Dr. Elizabeth Robertson** retired after 19 years at NIDA. Following an earlier career in research, teaching and federal service at the Department of Agriculture, Dr. Robertson joined NIDA in 1995. She served as the Chief of the Prevention Research Branch (PRB) from 1998 until 2011 and for the last three years has been Senior Advisor for Prevention Research. Dr. Robertson has been a leading advocate of a developmental, life course perspective on drug abuse prevention and she played a major role in fostering prevention services research to maximize the ways that effective prevention services would be available to the public. Dr. Robertson has been an advisor to the White House Office of National Drug Control Policy and a frequent consultant to many government and outside organizations. Dr. Robertson has always been a tireless advocate for prevention and the support of children and families. She developed and guided NIDA's prevention research program for more than 15 years.



## **GRANTEE HONORS**

**Dr. Annette Fleckenstein**, University of Utah, was elected president of the American Society for Pharmacology and Experimental Therapeutics. Her term begins July 1, 2014.

**Dr. Kenneth Kellar**, of Georgetown University's department of pharmacology, and a NIDA-funded grantee, has been named the recipient of the Society for Research in Nicotine and Tobacco's 2015 Langley Award, for his contributions to the field of nicotinic receptor research and addiction. The award will be presented at the Society's February 2015 annual meeting.

**Dr. Mary Jeanne Kreek**, Patrick E. and Beatrice M. Haggerty Professor, Head, Laboratory of the Biology of Addictive Diseases, and Senior Physician, The Rockefeller University Hospital, was presented with **NIDA's Lifetime Science Award** on May 6, 2014, *"In recognition of your pioneering efforts to bring methadone, the first medication for treating addiction, to the clinic; your seminal contributions to our understanding of addiction vulnerability and the neurobiology of opioid receptors; and your lifelong commitment to mentorship that has ensured the future of high quality addiction research."*

**Dr. R. Christopher Pierce**, received the Daniel H. Efron Research Award from ACNP (American College of Neuropsychopharmacology) at their meeting in December, 2013. The American College of Neuropsychopharmacology (ACNP) presents the Efron Award to an individual on the basis of outstanding basic research contributions to neuropsychopharmacology.

### **CTN Delaware Valley Node**

The **Christiana Care Health System** is a Community Treatment Provider (CTP) with the Delaware Valley Node. Project Engage is a product of the DVN/Christiana Care collaboration. **Project Engage** is being honored by the Professional Nurse Council in May at their annual meeting for "contributing significantly to the care of our patients and supporting nursing." It aims to identify patients hospitalized on medical/surgical wards that have a substance use problem and use peer counselors to get them into treatment.

### **CTN Florida Node Alliance**

**Dr. José Szapocznik**, (Co-PI) has been appointed by the Institute of Medicine of the National Academies to the National Research Council Forum on Promoting Children's Cognitive, Affective and Behavioral Health. The newly established forum aims to connect the prevention, treatment and implementation sciences with settings where children receive care, including healthcare facilities, schools, social service and child welfare agencies, the juvenile justice system and other community-based organizations. The forum will develop effective and affordable systems that address children's needs in these settings. Dr. Szapocznik, who is also Director of the Center for Family Studies and the Miami Clinical and Translational Science Institute at the University of Miami, welcomes the opportunity to contribute to a forum that will help improve the health of children.

### **CTN New England Consortium Node**

**Nancy Paull**, CEO of Stanley Street Treatment & Resources, Inc. (SSTAR) in Fall River, Massachusetts — a Community Treatment Program affiliated with the New England Consortium Node — was recently named a 2014 honoree for the National Council for Behavioral Health's Impact Award. The award is given to recognize organizations and leaders in the behavioral health field, committed to

providing community-based treatment to individuals with mental illnesses and substance use disorders. Nancy Paull was selected for a Visionary Leadership award. A celebration for the 2014 honorees will take place on May 6, 2014, in Washington, DC, at the time of the upcoming National Council Conference 2014. You can learn more about this award through the following link, <http://www.thenationalcouncil.org/about/awards/>.

**Dr. Samuel A. Ball**, professor of psychiatry at Yale University School of Medicine and an affiliated researcher with the New England Consortium Node and The APT Foundation, was recently named the president and chief executive officer of The National Center on Addiction and Substance Abuse (CASAColumbia®). CASA was founded in 1992 at Columbia University and has a mission to inform Americans of the economic and social costs of addiction and risky substance use and its impact on their lives; and to assess what works in prevention, treatment and disease management. Dr. Ball will retain his affiliation with Yale University School of Medicine and hopes to foster collaborations between CASAColumbia® and the Clinical Trials Network.

**Dr. Gene Brody** was inducted into the Honor Hall of Recognition by the University of Georgia at Athens College of Family and Consumer Sciences.

**Dr. Bruce Schackman** has been promoted to Professor of Public Health in the Department of Public Health at Weill Cornell Medical College.

#### **CTN Ohio Valley Node**

**Dr. Kathy Burlew** is being appointed as Fellow of the Graduate School at the University of Cincinnati. Dr. Burlew is the Principal Investigator of The Crossroads Center, a Community Treatment Program in the Ohio Valley Node and a Professor of Psychology at the University of Cincinnati. The Fellows of The Graduate School is an organization that recognizes distinguished researchers and scholars from throughout the University of Cincinnati. In addition to their outstanding individual accomplishments, Fellows are generally among the most experienced and accomplished graduate-student mentors at the University. New Fellows are elected annually by the current Fellows and are then appointed for life by the Board of Trustees. Criteria for election include evidence of outstanding scholarly and/or artistic attainment. The Fellows therefore constitute a significant resource of talent, experience and intellect at the university. Dr. Burlew will be honored at a ceremony in the Spring.

### **In Memoriam**

In March 2014, NIDA lost a colleague and friend, **Richard Denisco, M.D., MPH**. Richard joined the Services Research Branch in the Division of Epidemiology, Services, and Prevention Research in September 2005. He received his undergraduate degree from Emory University, his medical degree from the University of Florida, and was board certified in anesthesiology and pain medicine. He worked as an anesthesiologist and pain management specialist for many years. In 2005, he received his MPH from the Bloomberg School of Public Health at Johns Hopkins University. Richard was passionate about improving the lives of those struggling with substance use disorders. Drawing on his unique personal, professional, and medical expertise, he provided leadership for scientific initiatives emphasizing the delivery of smoking cessation, treatment of chronic pain, reduction of prescription drug abuse, and the training of physicians to effectively address addiction. He was an active member of several important NIH and federal groups focused on translating research into policies and practices to improve the lives of individuals. He received many accolades for his work including two NIH Director's awards for projects related to physician education. He gave his time, expertise, and ideas freely to others. He lived a life of noble service always seeking to relieve suffering and improve lives. He will indeed be missed.